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Estimation and Personalization of Clinical Insulin Therapy Parameters

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Estimation and Personalization of Clinical Insulin Therapy Parameters

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Estimation and Personalization of Clinical Insulin Therapy Parameters

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Despite considerable effort considerable cost in both time and money, as many as two out of three persons with type 1 diabetes are not in control of their disease. As a result, 40% of these individuals will go on to develop at least one serious complication including retinopathy, nephropathy, neuropathy and cardiomyopathy. It is further estimated that as much as $4 billion could be saved annually if all persons with type 1 diabetes in the US were properly controlled.

Adequate treatment of type 1 diabetes is predicated on the estimation of three clinical insulin therapy parameters: the basal dose, the insulin sensitivity factor and the insulin-to-carbohydrate ratio. Currently, these therapy parameters are determined by iterative titration procedures based on expert opinion. Unfortunately, there is evidence suggesting that for the majority of individuals, these titration protocols do not provide good results.

In this work we develop an alternative to traditional insulin titration protocols that allows clinical insulin therapy parameters to be estimated directly from a set of easily acquired measurements.

First, a simple model of type 1 diabetes is used to derive a series of equations connecting the model's parameters to the clinically important insulin therapy parameters

of insulin sensitivity factor, insulin-to-carbohydrate ratio and basal insulin dose. The simplifying assumptions used to derive these equations are tested and shown to be valid and the Fisher Information Matrix is used to demonstrate parameter identifiability.

Parameter estimation is then performed on two cohorts of virtual subjects, as well as two segments of real continuous glucose monitoring data from a person with type 1 diabetes. Identification of the true insulin therapy parameters is successful under most conditions for both cohorts of virtual subjects. Parameter estimation for one of the two segments of real continuous glucose monitoring data is also successful.

Finally, because continuous glucose monitors are instrumental to successful implementation of our insulin therapy framework, the physiological environment in which continuous glucose monitoring takes place is modeled and a fundamental limitation on measurement precision is shown to exist. An examination of physiological variability in the parameters indicates that many of the challenges observed in real world continuous glucose monitoring may have a relationship to changes in capillary bed perfusion. A rationale for anecdotally reported sensor faults is also proposed based on the physical mechanisms explored.

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Chapter 1: Introduction

Type 1 Diabetes Mellitus (T1DM), is an autoimmune disorder that affects over 1,000,000 individuals in the US, resulting in the destruction of the insulin-producing cells of the pancreas. Currently, the annual cost of T1DM in the US is $14.4 billion with $6.9 billion being spent on direct treatment costs and an additional $7.5 billion incurred as indirect costs [1]. Despite the considerable resources devoted to treating T1DM, more than 66% of Americans with T1DM fail to meet the American Diabetes Association's (ADA) standard for good control [2], [3]. As a result, countless individuals develop serious complications including retinopathy, nephropathy, cardiomyopathy, neuropathy and vascular disease [4]. As an example of the prevalence of these complications, as many as 30% of individuals with T1DM will develop full or partial blindness and as many as 40% will develop peripheral neuropathy which can lead to lower limb amputation [2].

Intensive Insulin Therapy and Titration

Forestalling or even preventing the development of these complications is possible by maintaining adequate glucose control. Two landmark studies, the Diabetes Control and Complications Trial (DCCT) [5] and the follow-up Epidemiology of Diabetes Intervention and Complications (EDIC) study [6] showed that intensive insulin therapy, with the goal of approaching near normal glycemia, significantly reduces the risk of nearly all diabetes related complications.

Presently, intensive insulin therapy involves the determination of three clinical therapy parameters. These parameters are: the basal insulin dose, which is the amount of long-acting insulin needed to ensure fasting euglycemia, the insulin sensitivity factor, which is the decrease in blood glucose following the injection of a single unit of rapid-

acting insulin and the insulin-to-carbohydrate ratio which is the dose of rapid-acting insulin needed to cover a specific number of carbohydrates [7].

Determining these clinical therapy parameters involves a process of titration wherein the appropriate dose of insulin is gradually determined through trial and error. The general approach to titration is to initiate therapy and then use a schema or algorithm to adjust the three insulin therapy parameters to reach a selected glycemic target. Some of these algorithms, such as the insulin titration protocol from the ADAPT trial [8] shown in Figure 1-1, clearly spell out what actions are to be taken under what circumstances. For example, given the ADAPT titration algorithm, if an individual has a fasting glucose value that exceeds 180 mg/dL, the protocol recommends that the dose of long-acting basal insulin be increased by 6 U. Other algorithms, such as the *Insulin Algorithm for Type 1 Diabetes Mellitus in Children and Adults* shown in Figure 1-2, provide glycemic guidelines, but do not recommend a specific action. In these cases, it is left to the physician to use his judgment when adjusting insulin therapy. A review of the literature reveals that while there are many guidelines for titration there does not appear to be a consensus on which algorithm is best. This is problematic because different titration algorithms can produce different therapy recommendations [9]. In addition, even for well-defined titration protocols such as the one used in the ADAPT titration algorithm [8], physicians often use their own judgment when adjusting insulin therapy.

Another significant problem is the convergence of these titration algorithms to a good treatment result. Because titration decisions often take place at intervals of three to six months, convergence of the algorithm to a good set of clinical therapy parameters may take an unacceptable amount of time. More problematically, because each algorithm is based on expert opinion, there is no guarantee that the algorithm will ever converge. This issue has been borne out by several clinical trials involving titration algorithms

where good control was achieved in only 14%, 25%, 32% and 38% of persons with T1DM following 28 weeks, 26 weeks, 52 weeks and 104 weeks respectively [8], [10]–[12].

CURRENT EFFORTS TO REPLACE OR IMPROVE INSULIN TITRATION

Several approaches have been taken to improve clinical outcomes for the many individuals with poorly controlled T1DM. Among these alternatives are those that augment or supplement titration and those that propose a new treatment paradigm or otherwise replace titration.

One augmentation to traditional insulin titration algorithms makes use of a tool called the ambulatory glucose profile (AGP) [13]–[15]. Discussed as far back as 1987, the ambulatory glucose profile is essentially a visualization tool that allows health care providers to more easily identify temporal patterns in an individual's blood glucose. When initially developed, the AGP was created using data from traditional glucometer readings. This required individuals to take four readings per hour each day over the course of 14 days [13]. By plotting these measurements a physician is able to observe blood glucose patterns and make insulin therapy adjustments accordingly.

At the time, this approach was limited by the fact that few patients are likely to adhere to such an intensive measurement schedule as well as by the need for equal or greater physician skill than required by traditional titration protocols. The availability of continuous glucose monitors has made the measurement burden less onerous, for the AGP as well as similar visualization techniques, but physician skill is still required to interpret the large volume of data [14], [16]. In addition, because the AGP is a tool to supplement physician decisions and not replace traditional titration, the length of time

needed to achieve good control may still be prohibitive assuming a three to six month delay between insulin adjustments.

In contrast, one replacement or substitute for traditional titration is closed-loop insulin delivery. Sometimes described as an artificial pancreas, closed-loop insulin delivery systems use continuous subcutaneous insulin infusion as well as continuous glucose measurements to automatically regulate blood glucose levels. A recent search on ClinicalTrials.gov for the term "artificial pancreas" reveals that at present, work on closed-loop insulin therapy is in an advanced state with 15 completed clinical trials, four clinical trials currently underway and 28 clinical trials in preparation. Further, in remarks made during the 2012 Barbara Davis Center Keystone Conference, John Pickup, MD (King's College London School of Medicine) indicated that both pumps and closed-loop algorithms are sufficiently optimized for closed-loop control [17].

However, in these same remarks Dr. Pickup highlights that the availability of reliable glucose sensing and improved insulin analogues currently limit the success of closed-loop insulin control [17]. In addition to these technical hurdles, the regulatory path for closed-loop insulin control is unclear and likely to be burdensome and development costs will likely exceed $170 million [17]. Further, even following regulatory approval, cost-effectiveness may still plague reimbursement, as it did with the continuous glucose monitor [18]. Finally, some individuals may be unwilling to switch to pump therapy because of personal preference or for psychosocial reasons. As it stands, insulin pumps are used by only 13% - 40% of persons with T1DM in the US and 5% - 15% of persons with T1DM in Europe [19], [20].

A third alternative that straddles the line between augmenting and replacing traditional titration algorithms is the decision support system. The development of new tools including decision support systems and clinical informatics has been identified as

one way to improve the outcomes of individuals with T1DM by several authors including those of the landmark Diabetes Attitudes, Wishes and Needs (DAWN) study [21], [22].

In principle, decision support systems can address the challenge of titration by lowering the requirement for provider skill and by allowing a physician to spend less of their already limited time pouring over an individual's recorded blood glucose measurements, a prerequisite for titrating insulin therapy [17].

Presently, at least one commercial decision support system for insulin titration, the Diabetes Insulin Guidance System (Hygeia, Inc., Ann Arbor, MI), is in development [23]. The Diabetes Insulin Guidance System is built on an algorithm that is intended to mimic the insulin titration recommendations of a skilled physician [23]. As a result, individuals with diabetes get the benefit of physician-led titration, but without the typical three to six month delay between titration decisions. However, this particular implementation of decision support would still suffer from the other shortcoming of titration, namely its inability to provide good control for as many as 62% of persons with T1DM [11].

Regardless of which approach is taken, successful replacement or improvement of current titration protocols would yield tremendous human and economic benefits. Looking at the human element, it is estimated that 920,000 additional years of eyesight, 691,000 additional years of kidney health and 678,000 additional years without lower limb amputation would result from universally good control of T1DM [22]. In addition, despite an increase in certain upfront costs, the total direct and indirect treatment costs for properly treated T1DM could drop by 8% and 50% respectively, yielding an annual savings of $4 billion in the US [1], [22].

RESEARCH OBJECTIVES

The overall goal of this work was to develop a novel method for estimating and personalizing clinical insulin therapy parameters. This method would form the basis for a decision support system that does not hew to existing insulin titration protocols. The ideal properties of this system include:

1. The ability to make good insulin therapy recommendations for most patients in a short time window—e.g., in a single physician visit as opposed to ten physician visits.
2. Little or no specialized training requirements for either physicians or patients.

To develop this system, the following approach was taken:

1. Select the simplest adequate model of T1DM and use it to derive closed-form expressions for the ideal basal dose, insulin sensitivity factor and insulin-to-carbohydrate ratio.
2. Analyze the model and these derived equations to evaluate both the uniqueness and the uncertainty of the insulin therapy parameters.
3. Demonstrate that the selected model can characterize the dynamics of T1DM and that the parameters in these closed-form expressions for ideal basal dose, insulin sensitivity factor and insulin-to-carbohydrate ratio can be accurately identified from simple experiments.
4. Evaluate whether likely measurement errors will introduce unacceptable variation or bias in the estimated insulin therapy parameters.

GUIDE TO CHAPTERS

Because this work may be of interest to both engineers and health care professionals, two separate chapters on background were included. In Chapter 2, we discuss the pathology, epidemiology and treatment of diabetes for those who are unfamiliar with the condition. In Chapter 3, we give a general exposition of the mathematical techniques used in this research which may be of interest to those without a background in mathematics and systems modeling. In Chapter 4, we derive the insulin sensitivity factor, insulin-to-carbohydrate ratio and basal insulin dose from the Bergman Minimal Model and consider both the uniqueness and uncertainty of these therapy parameters. In Chapter 5, we show that accurate estimates of these therapy parameters can be derived using self-reported meal and insulin logs and continuous glucose measurements. We also demonstrate that the model and insulin therapy framework proposed in Chapter 4 can be used to accurately estimate the insulin therapy parameters for much more complicated models of diabetes as well as real human data. In Chapter 6, we study the biology of the skin and determine whether physiological variations in subcutaneous glucose concentrations introduce unacceptable measurement errors to the required continuous glucose measurements. Finally, we close with Chapter 7 which includes conclusions and future work.

Titration Protocol from the ADAPT Trial

Individuals were treated with insulin detemir as their long-acting basal insulin and insulin aspart as their rapid-acting meal-time insulin.

Long-Acting Insulin Titration

if fasting glucose[1] value > 180 mg/dL	+ 6 U
if fasting glucose value 165 mg/dL – 180 mg/dL	+ 4 U
if fasting glucose value 145 mg/dL – 165 mg/dL	+ 3 U
if fasting glucose value 120 mg/dL – 145 mg/dL	+ 2 U
if any unexplained glucose values < 50 mg/dL	- 4 U
if any unexplained glucose values 50 mg/dL – 75 mg/dL	- 2 U

Rapid-Acting Insulin Titration

if post-prandial glucose[2] value > 270 mg/dL	+ 6 U
if post-prandial value 200 mg/dL – 270 mg/dL	+ 4 U
if post-prandial value 180 mg/dL – 200 mg/dL	+ 2 U

[1] For titration, the average of three measurements prior to physician visit were used.

[2] For titration, measurements were taken 1 - 1.5 hours post-meal. As with basal insulin titration, the average of three measurements prior to physician visit were used.

Figure 1-1: Titration Protocol from the ADAPT Trial

Insulin Algorithm for Type 1 Diabetes Mellitus in Children and Adults

This protocol is adapted from the January 2010 revision of *Insulin Algorithms for Type 1 Diabetes Mellitus in Children and Adults*, published by the Texas Department of State Health Services and the Texas Diabetes Council.

Consider referring all type 1 patients to pediatric/adult endocrinologist/comprehensive diabetes specialty team and consider continuous glucose monitoring

Basal Insulin: Glargine QD or Detemir QD-BID
Bolus Insulin: Regular Insulin, Insulin Aspart, Insulin Glulisine or Insulin Lispro before each meal

Premeal insulin dose includes:

1. Insulin to cover carbohydrates ingested; 1 unit Bolus Insulin covers 500/total daily insulin dose g-CHO
2. Additional insulin to correct for high self-monitored blood glucose; 1 unit Bolus Insulin lowers blood glucose by approximately 1800/total daily insulin mg/dL
3. Consider decreasing insulin by 1 U for every 30 minutes of preceding vigorous activity

Total Daily Insulin: 0.3 – 0.5 units/kg/day, titrate to achieve glycemic targets

Glycemic Goals

A1C	≤ 6 %	≤ 7 %	≤ 8 %
Fasting Plasma Glucose	≤ 110 mg/dL	120 mg/dL	140 mg/dL
Two-hour Post Prandial Glucose	≤ 130 mg/dL	180 mg/dL	180 mg/dL

Follow A1C Every 3-6 Months and Adjust Regimen to Maintain Glycemic Targets

Figure 1-2: Titration Guidelines from the Texas Diabetes Council

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Chapter 2: Physiological Background

In healthy individuals, cellular uptake and disposition of glucose, the primary substrate involved in cellular respiration, is controlled by a system of regulatory and counter regulatory hormones. Chief among these hormones is insulin which is produced in the beta cells of the pancreas. In diabetes, glucose metabolism is impaired by the body's inability produce insulin—as in type 1 diabetes mellitus (T1DM)—or by the body's insensitivity to insulin—as in type 2 diabetes mellitus (T2DM).

Below we will review the basic hormonal control which governs human glucose uptake. This will allow us to more clearly distinguish between the two primary varieties of Diabetes Mellitus, the pathology, prevalence and economic consequences of which are also discussed. Lastly, we will review the action and history of glucose measurement devices as well as insulin and insulin delivery devices.

GLUCOSE METABOLISM

All living things must eat to survive. In humans, digestion begins with salivary amylase, continues with action of gastric enzymes in the stomach and concludes with both pancreatic and natively secreted enzymes in the small intestine. The result is that proteins, fats and carbohydrates are digested or broken down into small peptides, fatty acids and monosaccharides and absorbed in the small intestine.

Utilization of these nutrients requires: bulk transport and diffusion to a given cellular surface, active or passive transportation across the cellular membrane and finally various transformations performed by a given cell's internal machinery.

Hormones control nearly every process in the body, including the regulation of nutrient supply and metabolism [1]. Cellular uptake of glucose is controlled primarily by insulin, produced by specialized beta cells located in the pancreas [2]. Insulin exerts its

influence by increasing the proportion of GLUT4—the primary glucose transport protein found in humans—present on a given cell's surface [3]. Glucose transport into the cell is followed rapidly by either utilization in ATP synthesis or storage as either glycogen in the skeletal muscles and liver or as fat in adipose tissue [4]. In mammals, up to 90% of all glucose metabolism is mediated and controlled by insulin, taking place in the skeletal muscles (75%) and adipose tissue (5-15%) [4]. Further, as transport across the cell membrane is the rate-limiting step in glucose utilization—except in the case of very high-levels of glucose utilization as might occur with vigorous physical activity—insulin is of singular importance in regulating the body's glucose levels [3].

Counterbalancing the action of insulin are both rapid-acting hormones, which include the catecholamines and glucagon, as well as slow-acting hormones which include cortisol and growth hormone [1], [5].

Among these hormones, glucagon is the clearest antagonist to insulin, increasing plasma glucose concentrations by stimulating glycogenolysis and gluconeogenesis in the liver [6]. The catecholamines act by suppressing the release of insulin, stimulating hepatic and renal gluconeogenesis, inhibiting peripheral glucose utilization and promoting the formation of ketone bodies, which can be used by the brain for energy, via lipolysis [5], [7]. Unlike glucagon and the catecholamines, which act to prevent acute hypoglycemia, cortisol and growth hormone are important in maintaining euglycemia during prolonged fasting [7]. Both cortisol and growth hormone act by promoting gluconeogenesis and lipolysis with growth hormone also suppressing peripheral glucose utilization.

DIABETES

Diabetes is a dysfunction of the body's glucoregulatory system. The two most prevalent forms of diabetes are T1DM and T2DM.

T1DM is an autoimmune disease of uncertain cause which typically results in a complete inability to produce insulin. T2DM by contrast is a disease of insulin resistance, wherein normal pancreatic function is initially maintained, but cellular sensitivity and responsiveness to insulin are diminished. For both diseases, severe long-term complications include coronary artery disease, peripheral vascular disease, stroke, cardiomyopathy, nephropathy, neuropathy and retinopathy [1].

As a note on nomenclature, in the past, T1DM has been referred to as both juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM), while T2DM has sometimes been described as either adult-onset diabetes or noninsulin-dependent diabetes mellitus (NIDDM). However, because both T1DM and T2DM can develop in either children or adults and because both T1DM and T2DM can be treated with insulin, these other names have begun to fall into disuse.

Type 1 Diabetes Mellitus

T1DM is the result of the autoimmune destruction of the insulin-producing beta cells of the pancreas [8]. Individuals begin to develop the obvious signs of T1DM following the destruction of 80% - 90% of the beta cells [8]. The destruction of the insulin-producing cells is absolute in most persons with diabetes, though limited beta cell function has been observed in some of the longest surviving persons with diabetes [9]. However, even in individuals with some residual beta cell function, in the absence of exogenous insulin, those with symptomatic T1DM will soon die as a result of diabetic ketoacidosis (DKA) [10].

In addition to preventing DKA, intensive insulin therapy, defined as treatment with the goal of achieving euglycemia or near-normal glycemia, has been shown to significantly reduce the risk of the long-term complications associated with T1DM [11]. The landmark Diabetes Control and Complications Trial (DCCT) [12] and follow-up Epidemiology of Diabetes Intervention and Complications (EDIC) study [13] showed that risks of retinopathy, nephropathy, neuropathy and cardiovascular disease could be reduced by as much as 76%, 50%, 60% and 57% respectively.

As of 2007, T1DM affected 850,000 – 1,700,000 individuals in the United States with an estimated direct medical cost of $6.9 billion and an estimated indirect cost of $7.5 billion [14].

Type 2 Diabetes Mellitus

By contrast, T2DM is a disease of insulin insensitivity. T2DM is also significantly more common than T1DM, affecting between 16 and 18 million individuals in the United States in 2012, and having a total treatment cost of $245 billion [15].

Most individuals initially present as obese or overweight and as a result the first-line therapy in T2DM is typically lifestyle changes, such as changes in diet and exercise [16]. While some individuals are able to halt the progression or even reverse the course of their disease through lifestyle changes, often oral drug therapy must be initiated to maintain control of the disease. However, if hyperglycemia cannot be controlled, insulin therapy is recommended by the American Diabetes Association [17].

GLUCOSE MEASUREMENT

In T1DM and T2DM treated with intensive insulin therapy the regular measurement of blood glucose levels, typically upon waking and before meals, is a crucial element in disease management [18]. The purpose of these measurements is to:

record data upon which health care providers can make therapy decisions for a patient, inform treatment decisions that may be flexible, such as adjusting the amount of insulin to be administered before a meal, detect hypoglycemia or hyperglycemia and provide immediate feedback to a patient about the effect of their lifestyle choices [19].

The most common tool for measuring blood glucose is the glucometer, which measures the concentration of glucose in a small blood sample—obtained with a lancet—electrochemically [20]. Outcomes in both T1DM and T2DM are generally better among patients who measure their blood glucose more frequently, though regular measurement is more important among insulin-treated persons with diabetes as both a means of making insulin dosing decisions and detecting hypoglycemia [19].

In addition to the discrete measurements provided by glucometers, continuous glucose measurements can be made using a continuous glucose monitoring (CGM) device. Presently, CGM devices are marketed by Abbott Diabetes Care, DexCom and Medtronic, though Abbott does not presently sell CGM systems in the US. Initial forecasts suggested that as many as 160,000 persons with diabetes in the US would be using continuous glucose monitors by 2009 [21]. However, due to issues with reimbursement and a lack of education among both patients and health care providers, adoption has been limited, with the total global user base in 2013 being 16,000 – 19,000 persons with diabetes [22], [23].

An important and related glycemic indicator used in the management of both T1DM and T2DM is that of A1C. A1C—sometimes referred to as HbA1c—is the percent glycosylation of hemoglobin in a sample of blood. Increasing blood glucose concentrations result in increased hemoglobin glycosylation and given the lifespan of hemoglobin, A1C is a proxy for average glycemia over the preceding 2 - 3 months [11]. High A1C has been linked to the development of long-term complications and is the

means *de rigueur* of assessing whether an individual's diabetes is properly controlled [11], [12]. In healthy individuals, A1C typically ranges between 4% - 6%, whereas per the ADA, a person with diabetes is considered in control if his or her A1C is below 7% [17].

INSULIN

Insulin was first discovered in 1922 by Frederick Banting, who went on to win the Novel Prize for his discovery [10]. The earliest commercial insulins were derived from the pancreatic extracts of various animals and while capable of preventing DKA, their clearance from the plasma was too rapid to provide good glycemic control [10]. It was not until 1946, when chemists at Nordisk were able to develop neutral protamine Hagedorn (NPH) or isophane insulin, the first intermediate-acting insulin, that good day-long control was possible [10]. Further refinement of NPH insulin, specifically the addition of zinc crystals to delay absorption from the subcutaneous injection site, produced the first long-acting insulins, lente and ultralente insulin [10].

Following the development of longer acting insulins, therapy moved in the direction of so-called basal/bolus protocols. The overall goal of basal/bolus protocols was to mimic physiological insulin levels seen in healthy individuals. This approach to insulin therapy called for a low baseline concentration of insulin to maintain fasting euglycemia with larger postprandial concentrations to prevent hyperglycemia following a meal [24]. This could be achieved by using either a mixture of rapid-acting regular insulin and NPH insulin immediately before a meal or by using a combination of long-acting ultralente once-daily with rapid-acting regular insulin being administered with each meal [24].

With the advent of recombinant insulin made by bacteria, the pharmacokinetics of insulin could be modified directly by making changes to the protein's sequence as opposed to indirectly through pH modifications or the addition of zinc as was done with NPH, lente and ultralente [24]. As a result regular human insulin has been largely replaced by insulin lispro—brand name Humalog—and insulin aspart—brand name Novolog—where rapid-acting insulin is appropriate and ultralente has been replaced by insulin glargine—brand name Lantus—and insulin determir—brand name Levemir.

While there has been some criticism of these newer analogues, suggesting that they cost significantly more than the drugs they replace without improving patient outcomes, it is at the very least agreed that they make treatment more convenient, especially in T1DM where multiple-daily injections of insulin are required [10], [25].

Insulin Administration Devices

Administration of insulin can be done with either a syringe or a pre-loaded pen. Insulin pens are available with a wide range of insulins and are generally preferred by patients as they are easier to use and less intimidating than a syringe [26]. This preference also results in improved adherence, better patient outcomes and lower total treatment costs [27].

As with glucose measurement, insulin administration can be done either discretely as with syringes and pens or continuously with a pump. There is conflicting evidence as to the advantage of insulin pumps—providing continuous subcutaneous insulin infusion (CSII)—over pens and syringes—used to provide multiple daily injection (MDI) therapy—with some studies suggesting there is no difference in outcomes [28] and others suggesting that CSII therapy provides a slight advantage over MDI therapy with respect to both A1C levels and the risk of hypoglycemia [29].

The annual treatment cost for insulin pump therapy is about the same as that of insulin pen therapy, averaging near $3,200 excluding the upfront cost of around $5,000 for the pump itself [28]. The use of syringes for MDI therapy is significantly less expensive at around $1,200 per year, but the benefit of improved patient adherence provides an indirect economic benefit, which exceeds the direct price difference [27], [28].

Despite the variety of drugs and devices available to treat both T1DM and T2DM, in aggregate, the evidence seems to suggest that highly motivated patients have good outcomes regardless of the type of insulin that they use or the method of administration [10], [30].

SUMMARY

Diabetes is a disease of the glucoregulatory system which either necessitates—as in T1DM—or often requires—as in T2DM—treatment with insulin. The goal of insulin therapy is to induce near-normal glycemia by mimicking the action of a healthy pancreas. Typically this entails the administration of a long-acting insulin analogue to produce so called basal control as well as various rapid-acting analogues to offset the effect of meals or other disturbances, such as illness or stress. Regular measurements of blood glucose concentrations with a glucometer are also required to monitor the body's response to meals and insulin so as to adapt therapy and detect hypoglycemia.

Avoiding the development of long-term complications, including damage to the heart, vasculature, kidneys, peripheral nervous system and eyes, is possible if average blood glucose concentrations are sufficiently close to those seen in healthy individuals. The trade-off being that intensive therapy, designed to produce near-normal glycemia, significantly increases the risk of iatrogenic hypoglycemia.

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Chapter 3: Mathematical Preliminaries

For those with backgrounds primarily in health care, we review some of aspects of pharmacokinetic (PK) and pharmacodynamic (PD) modeling as well as parameter estimation and epidemiological modeling. Readers who are familiar with these concepts may skip directly to subsequent chapters where the specific details of the present work will be discussed in depth.

PHARMACOKINETIC AND PHARMACODYNAMIC MODELING

Pharmacokinetic modeling is concerned with the absorption, distribution, metabolism and elimination of drugs and other compounds in the body, whereas pharmacodynamic modeling deals with the effects of these drugs on various biological processes [1]. By understanding how the discrete administration of a given drug affects the dynamic concentration of said drug and its metabolites, practitioners are able to screen new drugs for potential toxicity, extrapolate between animal and human models, ascertain what a typical dose should be and adjust drug regimens to account for complicating factors such as decreased kidney function or co-administration of interacting drugs [2]. As a result, PK/PD modeling is important to pharmaceutical chemists, health care professionals and patients.

Generally, PK modeling is somewhat separate from PD modeling as it is easier to measure the concentration of a drug than its effect. PK modeling is approached from one of several avenues including: compartmental modeling, noncompartmental modeling, physiological modeling or population modeling, depending on the drug in question and the aims of the researcher [1].

In compartmental modeling, one hypothesizes that a drug is distributed throughout a series of compartments. Linear ordinary differential equations are typically

used to describe a mass balance across these compartments, which means that the connection between dose size and observed concentration will be a sum of exponentials.

Noncompartmental modeling looks at information that can be derived directly from the data and treats these measurements as outputs of the administered dose. Examples of the modeled outputs of a noncompartmental model include: area under the curve for a time series of concentration measurements, the maximum drug concentration for a given dose and the time required to reach this maximum concentration. This type of modeling is often used to show bioequivalence between two formulations of the same active pharmaceutical ingredient as is required for the FDA approval of some generic drugs.

Physiologically-based pharmacokinetic (PBPK) models are similar to compartmental models with the exception that each compartment corresponds to a tissue, organ system, cellular site or other physiologically meaningful location within the body. PBPK models are advantageous in that they can be used to answer important physiological questions including for example, the effect of decreased renal clearance or lung capacity on the concentration and effect of a drug throughout the body. PBPK are however more difficult to develop and validate than compartmental models as they typically require measurements of drug concentration throughout the tissues being modeled or the cobbling together of sub-models of each organ system from the literature. Further, collecting the data required to develop a PBPK model may require uncomfortable measurement procedures—including the measurement of exhaled gases or the performance of tissue biopsies—or the administration of radio-labeled drugs.

Lastly, population PK models essentially pool together the PK data from several subjects to understand how each model parameter is distributed across a population. This

kind of analysis can be very important when determining appropriate dosages for a novel pharmaceutical compound.

Mapping drug concentrations to drug effects is done by linking a PK model to a PD model. Generally, this is done by either appending an effect compartment to the dynamic PK model or by modeling the effect as a static nonlinear function of the drug concentration in one of the PK compartments [1]. If an effect compartment is to be used, the assumption of first order linear kinetics often holds, though nonlinear models are common and include Hill kinetics or Michaelis-Menten kinetics [1].

IDENTIFIABILITY AND PARAMETER ESTIMATION

The problem of parameter estimation is in some sense three-fold. First, for a given model structure is there any set of inputs and observations that allow one to uniquely identify the values of each model parameter. This is known as the problem of structural identifiability. Second, given the particular set of inputs and observations for which you have collected data, is it possible to uniquely identify the values of each model parameter. This is known as the problem of informational identifiability and is closely related to so-called persistency of excitation. Finally, given the errors in your data and your computational resources is it possible for you to numerically estimate the values of these model parameters. This is what is typically thought of as parameter estimation or the inverse problem.

The general theory of identifiability, describing the necessary and sufficient conditions for both structural and informational identifiability, is well-developed. The following outline is adapted from Ljung *et al.* [3]

Let us consider the typical state-space model:

$$\dot{x} = f(x(t), u(t), \theta), \qquad x(0) = x_0 \tag{3.1}$$

$$y(t) = h(x(t), u(t), \theta). \tag{3.2}$$

Where x corresponds to some unobserved states, u corresponds to known inputs, y corresponds to known measurements and θ is the vector of parameters we would like to estimate.

By definition, if this model is structurally identifiable given some set of inputs u and some initial condition x_o, the outputs y will be differ for each parameter vector θ. More formally, if a model is structurally identifiable the following statement is true:

$$\forall \theta \in P, \exists\, u: y(x, u, \theta) = y(x, u, \theta^*), iff\ \theta = \theta^*, \tag{3.3}$$

where P is the space of all possible parameter values.

A necessary and sufficient condition for the structural identifiability of our model is given by:

$$P_i(u, y)\theta_i - Q_i(u, y) = 0, \qquad i = 1, \dots, d, \tag{3.4}$$

where P_i and Q_i are functions of only u and y formed by differentiating, adding and subtracting or scaling and multiplying the combined set of Equations 3.1 and 3.2 and θ_i is the i^{th} element of the d-dimensional vector θ. Equation 3.4 also serves as a necessary and sufficient condition on informational identifiability, namely, a set of inputs u producing outputs y is persistently exciting if and only if P_i is non-zero for all i.

Actually verifying that Equation 3.4 holds for a given model system is normally a very difficult task except. When dealing with biological systems this is doubly true as many of the body's states are difficult or impossible to observe and to increase the robustness of an organism biological systems exhibit a large amount of redundancy [4], [5]. In principle, the question can be answered by one of several methods including the Taylor Series approach, the Generating Series approach, the Similarity Transform approach or the Differential Algebra approach [6]. However, even in the case of linear compartmental models, each of these approaches requires the symbolic solution of complex nonlinear equations and if possible it is preferable to work with one of the families of models for which proofs about identifiability exist [7].

Once the identifiability of a model has been established parameter estimation techniques are used to identify the values of θ by minimizing some objective function of the parameters, typically, the sum of square errors:

$$J(\theta) = \int_0^T \left(y_{obs} - \hat{y}(t)\right)^2 dt, \tag{3.5}$$

where y_{obs} is the measured output and $\hat{y}(t)$ is the solution to Equation 3.2.

Due to measurement noise, the surface $J(\theta)$ is typically rough and finding the parameter vector θ that would otherwise be the global minimizer may be challenging. In addition, as posed each iterative solution of $J(\theta)$ will require numerical integration of 3.1 and 3.2 making this problem computationally intensive.

One way to sidestep some of the challenges described above is by using a technique called principal differential analysis (PDA). In PDA, one fits a basis function to the data, typically a spline, and then uses this basis function to calculate the derivatives

directly [8], [9]. As a result, if all the states in Equation 3.1 are observed—i.e. if $y = x$ in Equation 3.2—one can minimize the following in place of Equation 3.5:

$$J(\theta) = \int_0^T \left(\dot{y}_{spline} - \dot{y}(t)\right)^2 dt. \tag{3.6}$$

While the ability to observe every state, especially in a biological system may seem restrictive, we will see that for some models of diabetes this requirement can be satisfied.

EPIDEMIOLOGICAL MODELING

According to the WHO, epidemiology is the study of the distribution and determinants of health-related states or events. Epidemiological modeling gives us a way to map the effect of drug therapies or other interventions at the individual level to the development of long-term complications.

Epidemiological modeling requires first that we have a PK/PD model for a given disease. We next must assume or otherwise determine the population level distribution of the parameters governing our model. Combining these two models allows us to evaluate how a given treatment policy, e.g. the administration of a 300 mg of a drug three-times daily, will effect a simulated patient population. We next need a risk model that links either the outputs of the PK/PD model or some transformation thereof, e.g. average HDL levels over a given time interval, to the development of various disease states. For comparison of some drug therapies this may be sufficient, especially where there is one dominant complication the therapy is designed to prevent. However, in the case of a disease with several severe complications such as diabetes, it is also helpful to have an

economic model that will allow us to calculate the expected loss associated with different complication profiles across compared therapies.

Epidemiological modeling of this kind is already prevalent in determining reimbursement for drug therapies [10], replacing animal trials [11] and designing subsequent human trials [12].

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Chapter 4: Treatment Decisions from Mathematical Models of Diabetes

Mathematical modeling of the glucoregulatory system has been an active area of research for over forty years [1]–[3]. The majority of work done by the controls community has focused on the development of closed-loop control with insulin pumps, referred to as the artificial pancreas. Despite being an important area of research, among persons with T1DM, pump adoption has been limited in both the US and Europe.

As a result, there is a clear need to connect existing models of diabetes with the treatment parameters used by someone on MDI therapy. These treatment parameters are the basal insulin dose, the insulin sensitivity factor (ISF)—which is the drop in blood glucose caused by a unit of rapid-acting insulin—and the insulin to carbohydrate ratio (I2C)—which governs the amount of insulin needed to prevent post-prandial hyperglycemia [4].

In this chapter we derive a simple control law based on the eponymous Bergman Minimal Model (BMM) [5]. The accuracy, limitations and underlying assumptions of this control law are discussed and a connection between the clinical MDI parameters of basal dose, ISF and I2C is made. The Fisher Information Matrix (FIM) is used to establish *a posteriori* identifiability of the model under home-use conditions. Lastly, the sensitivity of the controller to both parameter and input uncertainty is discussed.

MODELING ENVIRONMENT

Bergman Minimal Model

The BMM was first proposed for the purposes of modeling glucose disappearance following an intravenous glucose tolerance test (IVGTT). It was originally described as a two compartment model, with one compartment (G) describing the concentration of glucose in the plasma and a second (X) describing the remote action of insulin. As

formulated however, there is an implicit third compartment corresponding to the plasma insulin (I). Here we have also included a term corresponding to the mass of carbohydrates in the gut (G_{gut}) allowing us to model the effect of meals on blood glucose concentrations.

$$\dot{G} = -p_1(G - G_b) - S_i X G + \frac{f k_{abs}}{V_G} G_{gut} \tag{4.1}$$

$$\dot{X} = -p_2(X - I - I_b) \tag{4.2}$$

$$\dot{I} = u - k_e I \tag{4.3}$$

The terms in Equation 4.1 are: p_1 the glucose effectiveness; G_b the basal, or steady-state plasma glucose; S_i the insulin effectiveness; f the fraction of meal carbohydrates that are available for absorption from the gut; k_{abs} the rate at which carbohydrates are absorbed into the blood stream from the gut and V_G the volume of plasma glucose distribution. The terms in Equation4.2 are: p_2 the fractional rate of remote insulin clearance and I_b the basal plasma insulin concentration. Lastly, the terms in Equation 4.3 are u the rate of insulin infusion or absorption into the plasma from an exogenous input and k_e the clearance rate of insulin from the plasma.

Subcutaneous Insulin Injection Model

Numerous models have been proposed to describe the concentration of plasma insulin following subcutaneous injections. One of the earliest models, proposed by Berger and Rodbard [6], is shown below in Equation 4.4.

$$\dot{I} = \frac{st^{s-1}T_{50}^{s-1}}{V_i(T_{50}^s + t^s)^2} I_d - k_e I \tag{4.4}$$

Originally proposed to deal with early insulins such as NPH, lente and ultralente this model includes two insulin specific parameters *s*, an empirically determined scalar and T_{50} the time needed for 50% of the injected insulin to be absorbed into the plasma, as well as two generic parameters k_e, which as before is the rate of insulin clearance from the plasma and V_i the distribution volume of insulin within the plasma. While compact, the model is cumbersome in that it has a highly nonlinear insulin input term. Further, recent work to extend this model to modern insulins, such as insulin aspart, is somewhat suspect, predicting an insulin distribution volume of 135L [7].

For this reason, we have chosen to model the injection of rapid-acting insulin as an impulse and the injection of long-acting insulin as a step-function as shown below in Equation 4.5 and Equation 4.6.

$$u_{rapid} = \frac{I_d}{V_i}\delta(t) \tag{4.5}$$

$$u_{long} = \begin{cases} \frac{I_d}{V_i t_a}, & 0 < t < \mathrm{t_a} \\ 0, & \mathrm{t} \geq \mathrm{t_a} \end{cases} \tag{4.6}$$

The terms in Equation 4.5 are the size of the insulin dose I_d and the distribution volume of insulin in the plasma V_i. Equation 4.6 contains an additional term t_a which is the length of time that a dose of long-acting insulin remains active. For an ideal peakless once-per-day insulin, this would be 24 hours. Equation 4.5 and Equation 4.6 are used to model the input *u* to Equation 4.3.

Meal Model

Using data from 41 subjects, Dalla Man et al. [8] developed and validated a model of the gastric system which is described below in Equations 4.7 - 4.12.

$$\dot{q}_1 = u - k_{emp} q_1 \tag{4.7}$$

$$\dot{q}_2 = k_{emp}(q_1 - q_2) \tag{4.8}$$

$$\dot{G}_{gut} = k_{emp} q_2 - k_{abs} G_{gut} \tag{4.9}$$

Terms in Equation 4.7 are: q_1 the mass of carbohydrate in stomach compartment one, u the meal input and k_{emp} the rate constant for gastric emptying. Terms in Equation 4.8 are: q_2 the mass of carbohydrate in stomach compartment two and k_{abs} the rate constant for carbohydrate absorption from the gut. Finally, Equation 4.9 describes the mass of carbohydrates in the gut which is given by G_{gut}.

Meals are modeled as the impulse response to Equation 4.7 – 4.9. The impulse response for this coupled system is given in Equation 4.10 for a meal of containing a mass of carbohydrates D.

$$G_{gut} = D\left[\beta e^{-k_{abs}t} - (\beta + \gamma t) e^{-k_{emp}t}\right] \tag{4.10}$$

$$\beta = \frac{k_{emp}^2}{\left(k_{emp} - k_{abs}\right)^2} \tag{4.11}$$

$$\gamma = \frac{k_{emp}^2}{\left(k_{emp} - k_{abs}\right)} \tag{4.12}$$

Taken as a whole, Equations 4.1 – 4.3 and Equations 4.5 – 4.9 form the Extended Bergman Minimal Model (EBMM).

CLINICAL INSULIN THERAPY PARAMETERS

We concern ourselves now with the derivation of the insulin sensitivity factor, insulin-to-carbohydrate ratio and basal dose using the EBMM.

Insulin Sensitivity Factor

In the absence of any meals and assuming a steady-state we set the left-hand of both Equation 4.1 and Equation 4.2 to zero and find:

$$G = \frac{p_1 G_b}{p_1 + S_i X'}, \tag{4.13}$$

$$X = I - I_b. \tag{4.14}$$

Given that the EBMM treats insulin as deviations from a baseline concentration, Equation 4.13 allows us to calculate the effect of additional rapid-acting insulin on glycemia. If we approximate the appearance of rapid-acting insulin following an injection of size I_d as a step increase in the plasma insulin with some time length t_a in an insulin distribution volume V_I then:

$$I - I_b = \frac{I_d}{V_I k_e t_a}. \tag{4.15}$$

Finally, we can calculate the ISF by using Equation 4.13 and noting that:

$$\Delta G \equiv G_f - G_b = \frac{p_1 G_b}{p_1 + S_i X} - G_b = G_b \frac{Ba}{1 + Ba}, \tag{4.16}$$

$$Ba \equiv \frac{S_I I_d}{p_1 V_i k_e t_a}, \tag{4.17}$$

$$ISF = \frac{\Delta G}{I_d}, \tag{4.18}$$

where we have defined the Banting Number, a dimensionless plasma insulin concentration, as *Ba* in honor of Frederick Banting, that accounts for the kinetics of both glucose and insulin disposition in Equation 4.17.

Insulin-to-Carbohydrate Ratio

Next, we note that per Equation 4.1, preventing post-prandial hyperglycemia can be accomplished if:

$$S_i I G_b = \frac{f k_{abs}}{V_G} G_{gut}. \tag{4.19}$$

Assuming similar kinetics for the appearance of food in the gut and insulin in the plasma following a meal and insulin injection, we find that the I2C is given by:

$$I2C = \frac{D}{I_d} = \frac{S_I V_G}{f k_{abs} V_I} G_b. \tag{4.20}$$

Basal Insulin Dose

Finally, to calculate the basal dose we make reference to Equation 4.15 and note that the basal insulin dose is given by:

$$I_d = V_i k_e t_a I_b. \tag{4.21}$$

Equation 4.21 would be most appropriate for initiating new insulin therapy, for modifying an existing insulin regimen it is sufficient to use Equations 4.16 – 4.18

ACCURACY, LIMITATIONS AND ASSUMPTIONS

Dynamic Simplification

Looking at Equations 4.13 and 4.19 we have exact relationships algebraic relationships relating the various states of our model to one another. However, in developing the therapy calculators of Equation 4.18, Equation 4.20 and Equation 4.21—which constitute a kind of static input/output model—we have made numerous simplifying assumptions to the dynamic EBMM.

To assess the effect of this dynamic simplification we have constructed three test simulations which are shown in Figures 1 – 3. Each test simulation was performed using the same parameter vector—shown in Table 4-1—and Equations 4.1 – 4.9. Numerical integration was performed using ode45 in MATLAB 2010b. All simulations were initialized at steady-state—i.e., $G=G_b$ and $I=X=I_b$.

To assess the validity of the approximations used in deriving the insulin sensitivity factor given by Equation 4.18, the glucose response to an injection of 0.1 U, 0.5 U, 1.0 U and 2.0 U was simulated over a course of 12 hours. Referring to Table 4-1 we see that per Equation 4.18 we have calculated an ISF of 45 mg/dL-U for this patient.

Looking at Figure 4-1, we see that for insulin doses of 0.1 U and 0.5 U the observed ISF is approximately 50 mg/dL-U, for the administration of 1.0 U of insulin the apparent ISF is 38 mg/dL-U and that for the administration of 2.0 U of insulin the apparent ISF is 29 mg/dL-U. It is thus clear that for small insulin doses, up to perhaps 1.0 U or slightly more, the dynamic simplifications in Equation 4.18 hold.

Further, in arriving at an ISF of 45 mg/dL-U we have used the definition of the insulin sensitivity factor, as the drop in blood glucose brought about by a single unit of rapid-acting insulin, in Equation 4.16. Building on Equation 4.16 and Equation 4.17, we now define a dimensionless blood glucose correction factor *Co*:

$$\mathrm{Co} \equiv \frac{\Delta G}{G_b} = -\frac{Ba}{1 + Ba}. \tag{4.22}$$

Plotting the above in Figure 4-3 it is clear that *Co* is a nonlinear function of the dimensionless insulin concentration *Ba*. As a result, ISF must also be a nonlinear function of *Ba*. Noting this relationship, and using the parameters in Table 4-1, the ISF for 2 U of insulin is calculated to be 28 mg/dL-U in excellent agreement with the simulated result.

As such, we see that the dynamic simplifications made to arrive at Equation 4.18 are in fact quite robust. Using Equation 4.18, the ISF can either be approximated with a linear scaling factor for small doses of insulin or calculated using the full nonlinear relationship for larger doses of insulin.

To evaluate post-prandial glucose control using the insulin-to-carbohydrate ratio from Equation 4.29, we looked at the effect of a 70 g-CHO meal with and without the concurrent administration of 1.5 U of rapid-acting insulin. The resulting blood glucose

trace is shown in in Figure 4-2. In the absence of any insulin, post-prandial hyperglycemia is severe, peaking at 245 mg/dL and remaining above 140 mg/dL for at least three hours. By contrast, when 1.5 U of insulin is administered along with the meal, glucose never rises above 120 mg/dL and bottoms out around 80 mg/dL. From Table 4-1, we see that the apparent I2C is 52 g-CHO/U implying that 1.35 U of insulin are needed to cover the meal. The remaining 0.15 U should produce a blood-glucose drop of 7 mg/dL using the linear ISF or 10 mg/dL per the full nonlinear ISF. However, we see that post-prandial glucose is depressed by as much as 20 mg/dL. Thus, our dynamic simplification has introduced some error into the estimation of I2C. However, as the discrepancy is relatively small, at 10 mg/dL, we feel that this source of error is negligible.

We also, we wish to point out the role of insulin timing in proper glucose control. Tacitly, we have assumed that insulin administration should occur alongside each meal. However, it is commonly accepted that administering insulin prior to a meal can actually improve post-prandial glucose control and lower the risk of hypoglycaemia. Shown in Figure 4-4 is the effect of administering rapid-acting insulin 15 minutes prior to each of three meals. While both concurrent and prior administration of insulin is able to prevent post-prandial hyperglycemia, prior administration keeps blood glucose in a tighter band, having no excursions above 120 mg/dL and no excursions below 80 mg/dL. By comparison concurrent administration of insulin allows post-prandial glucose to rise as high as 140 mg/dL and induces the patient to spend a significant amount of time at or near 75 mg/dL, a threshold value for some definitions of hypoglycaemia. While it may not always be convenient for patients to do so and while our model does not explicitly account for optimal administration time, the advantages of early insulin administration are clear.

Finally, the approximation error introduced in our determination of the basal insulin dose is considered to be negligible as a series of ideal long-acting insulin injections would produce a totally flat profile as given by Equation 4.21.

Identifiability

As mentioned in previous chapters, identifiability is an important but often difficult to assess property of any model.

Having mapped the EBMM to clinically relevant MDI parameters, we now wish to determine two things. First, given home-use conditions is this model identifiable and second, if so how does uncertainty in model parameters propagate through to the insulin therapy recommendations.

Experimental Conditions

To answer this question we must first simulate home-use conditions and then perform sensitivity analysis on the EBMM.

For all simulations, the EBMM was initialized with representative parameters reported in the literature and found in Table 4-1. As before, the equations were numerically integrated in MATLAB 2010b using ode 45. A twenty-four hour period was then simulated wherein the virtual patient awoke at 7:00 am and then consumed a total of 200 g of carbohydrates in meals of equal size at 8:00 am, 12:00 pm, and 8:00 pm. The prandial insulin dose was calculated using a linear ISF from Equation 4.20 and administered concurrent with the meal. The basal insulin requirement was calculated using Equation 4.21. Simulated glucose measurements were recorded using the above procedure with a ten-minute sampling of blood glucose without noise. The results of this experiment are shown in Figure 4-5.

Fisher Information Matrix

The Fisher Information Matrix—defined in Equation 4.25—allows us to estimate the variance of a given model parameterization from the sensitivity vector defined in Equation 4.23.

$$S_{ij}(t) = \frac{dx_i(t)}{dp_j}. \tag{4.23}$$

Using the simulated measurements described above as well as the central difference approximation in Equation 4.24 the sensitivity coefficients were calculated and stored [9].

$$S_{ij}(t_k) \approx \frac{x_i(t_k)|_{p_j+\Delta p_j} - x_i(t_k)|_{p_j-\Delta p_j}}{2\Delta p_j} \tag{4.24}$$

All parameters in the EBMM were perturbed 1% from their nominal value to evaluate Equation 4.24.

The sensitivity vectors were then used to calculate the Fisher Information Matrix, which is given by:

$$FIM = \sum_{k=1}^{N_t} S^T(t_k)R^{-1}(t_k)S(t_k), \tag{4.25}$$

where R is the state covariance matrix. As only a single state is under consideration R is the variance of the glucose measurements, which was assumed to be 100 $(mg/dl)^2$.

The Cramer Rao Bound allows us to find a lower bound for the parameter variance from the Fisher Information Matrix:

$$\sigma_{p_j}^2 \geq FIM^{-1}{}_{jj}. \tag{4.26}$$

Finally, assuming that all parameters must be greater than zero gives us an approximate necessary condition for the model's *a posteriori* parameter identifiability; namely $p_j > 1.96\sigma_j$. This ensures that the 95% confidence interval for p_j does not contain zero.

Results of the sensitivity analysis are presented in Table 4-1 and demonstrate that the model is identifiable under the given conditions. For all parameters, the coefficient of variation as calculated by the FIM is less than 9% meaning that the value zero is at least 11 standard deviations away from the nominal parameter estimate.

To examine the identifiability of the EBMM over a larger parameter space, 150 random parameter vectors were generated where each element in the vector was given by a uniformly distributed random number that was +/- 30% of the nominal parameters in Table 4-1. The identifiability analysis described above was repeated and the results are presented in Figure 4-6. As before, all parameters are identifiable.

Given that the meal and insulin inputs were selected to cancel each out, the simulated experiment is nearly as uninformative as is possible. This fact, coupled with the identifiability of the model over a large swath of parameterizations, allows us to move forward with good confidence that the EBMM and the parameters in Equation 4.18, Equation 4.20 and Equation 4.21 will be identifiable in most circumstances.

Propagation of Errors

Having demonstrated identifiability of the EBMM, we now turn to the question of uncertainty in our therapy recommendations. Parametric uncertainty in the EBMM will propagate through Equation 4.18, Equation 4.20 and Equation 4.21 and may produce undesirable controller performance. The variances of the I2C and basal dose as determined from Equation 4.20 and Equation 4.21 are given by the following equations:

$$\sigma_{I2C}^2 = \left(\frac{G_b}{f k_{abs}}\right)^2 \sigma_{S_i}^2 + \left(\frac{S_I}{f k_{abs}}\right)^2 \sigma_{G_b}^2 + \left(\frac{S_I}{f^2 k_{abs}} G_b\right)^2 \sigma_f^2 + \left(\frac{S_I}{f k_{abs}^2} G_b\right)^2 \sigma_{k_{abs}}^2, \tag{4.27}$$

$$\sigma_{I_{d,basal}}^2 = (V_i k_e t_a)^2 \sigma_{I_b}^2 + (V_i t_a I_b)^2 \sigma_{k_{k_e}}^2 + (k_e t_a I_b)^2 \sigma_{V_i}^2. \tag{4.28}$$

Evaluating Equation 4.27 and Equation 4.28 for the parameters in Table 4-1, the coefficient of variation for I2C is 10.4% and the coefficient of variation for $I_{d,basal}$ is 6.3%. The coefficient of variation for ISF was evaluated numerically using MAXIMA, a computer algebra program, and has a value of 9.0%.

Uncertainty in ISF is due almost entirely to the uncertainty in G_b. While the other parameters in Equation 4.16 and Equation 4.17 would be difficult to estimate in a home-use setting, G_b could be estimated from a measurement of fasting blood glucose in the morning. Doing so could reduce the coefficient of variation to 4.2% if the measurement was sufficiently precise.

The uncertainty in I2C is dominated by the second and fourth terms in Equation 4.27. As with ISF, it is difficult if not impossible to observe k_{abs} under home-use

conditions, however, estimating G_b directly from a fasting blood glucose measurement in the morning could reduce the coefficient of variation of I2C to as little as 3.3%.

Uncertainty in $I_{d,basal}$ is dominated by the first term in Equation 4.28. Unfortunately, unlike with I2C, there does not appear to be an easy way to reduce this uncertainty with supplementary observations. However, as the standard error is already small, this uncertainty is acceptable for our purposes.

SUMMARY AND CONCLUSIONS

In this chapter we have developed aconnection between the EBMM and the clinically significant insulin therapy parameters of ISF, I2C and basal dose. For a representative set of model parameters, these treatment parameters were found to be 45 mg/dL-U, 52 g-CHO/U and 12.6 U respectively. These estimates for ISF and basal dose are in excellent agreement with values commonly used to treat T1DM [10], [11]. By contrast, the calculated value for I2C is a factor of 2-5 times higher than might be seen in practice. This is attributed to the limitations of our meal model as well as the value of the nominal parameters.

Using the Fisher Information Matrix we have shown that the EBMM is identifiable under home-use/ambulatory conditions from a stream of continuous glucose measurements. This result was robust across a large range of parameter values and is necessary to determine patient-specific insulin therapy parameters by fitting the EBMM to a patient-specific data set.

Lastly, the effect of uncertainty in the model parameterization on the calculation of ISF, I2C and the basal dose was evaluated. The coefficients of variation for ISF, I2C and basal dose were found to be: 9.0%, 10.4% and 6.3% respectively. The coefficients of variation for ISF and I2C could be further reduced to 4.2% and 3.3% respectively given a

sufficiently precise measurement of the fasting plasma glucose. Given the limitations of insulin pens, which are rated to deliver small doses with an accuracy of +/- 10% and can at best deliver insulin in increments of 0.5 U [12], and that individuals tend to overestimate carb intake by as much as 20% [13], the effect of parameter uncertainty on controller performance appears to be acceptable.

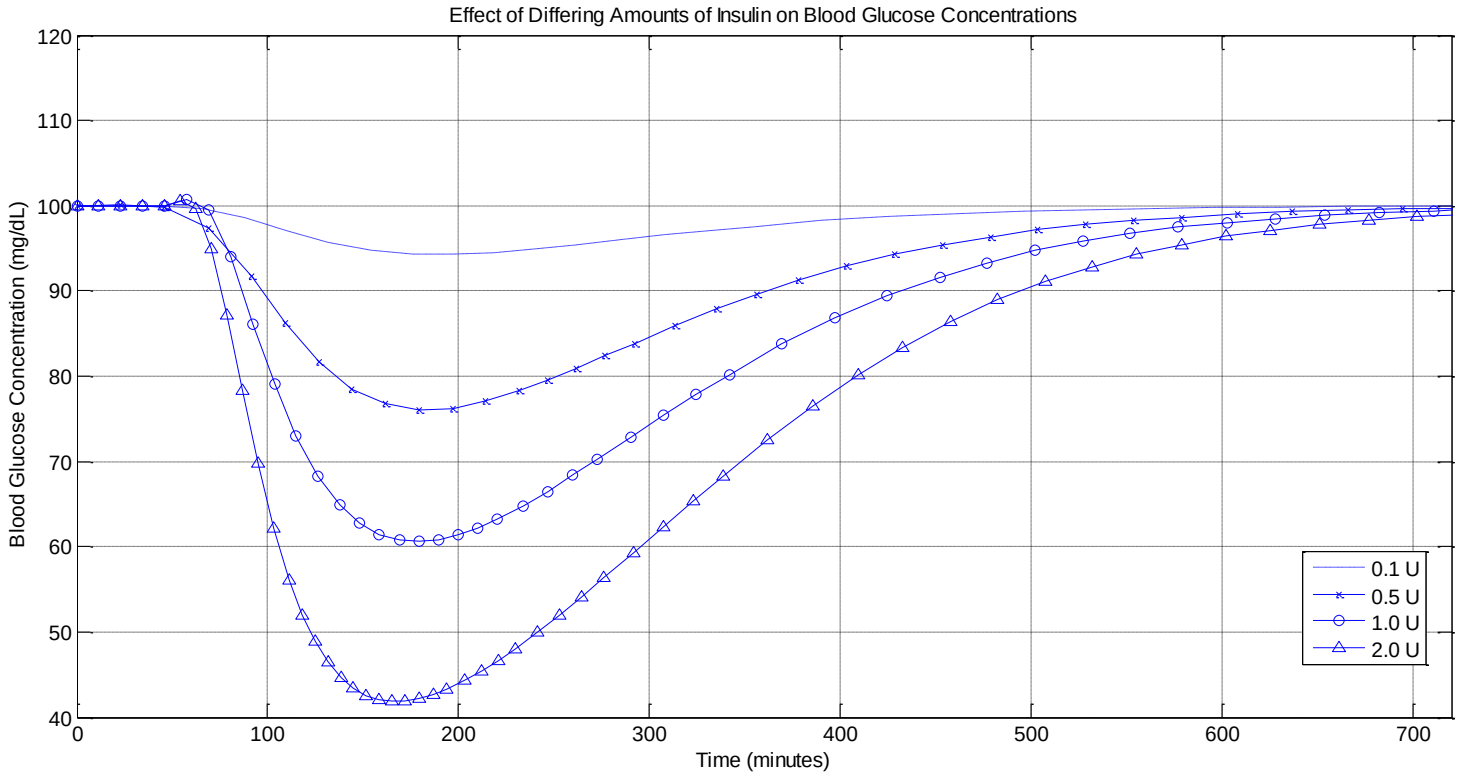

Figure 4-1: Effect of Rapid-Acting Insulin on Plasma Glucose Concentrations

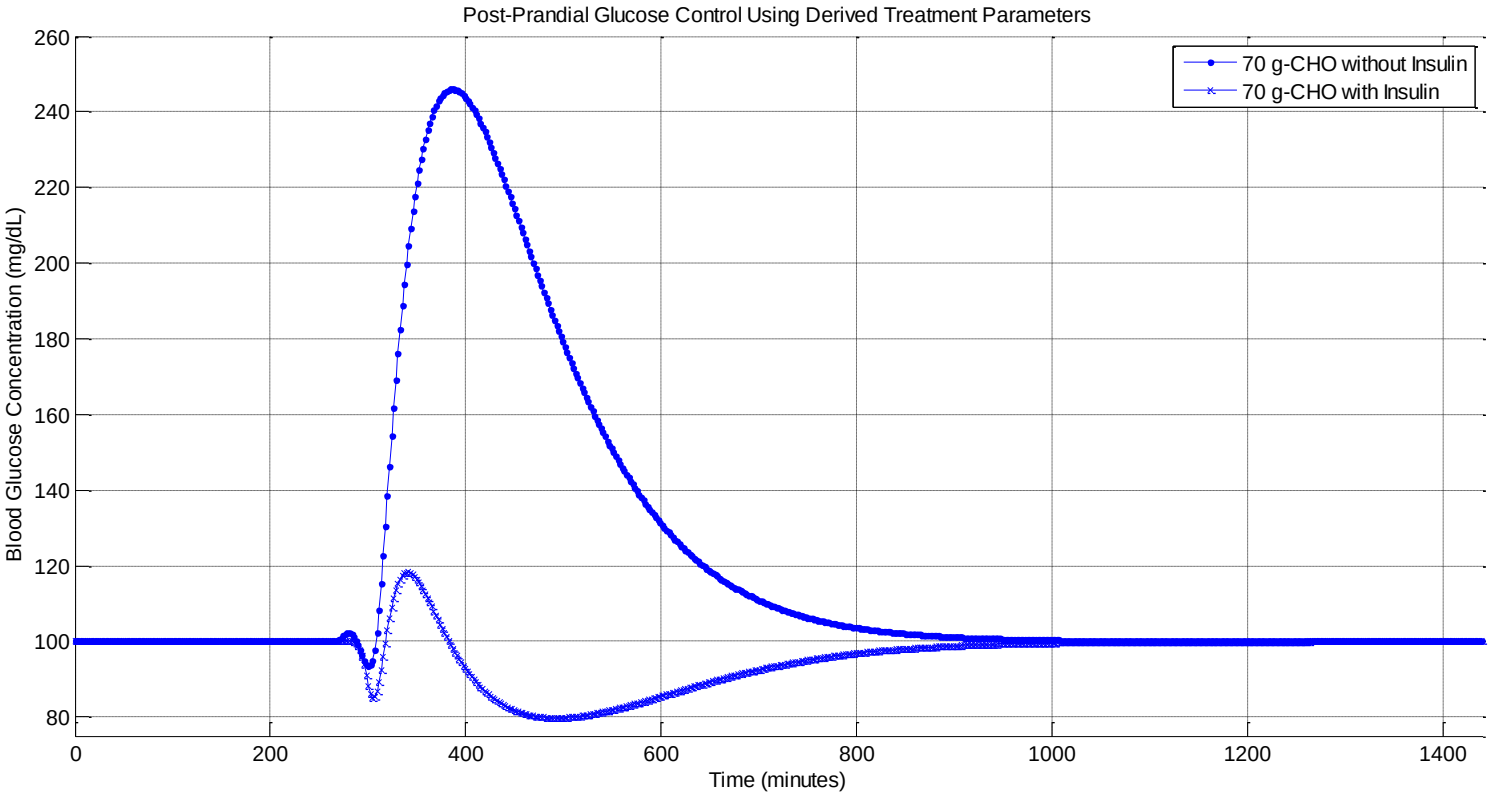

Figure 4-2: Effect of Rapid-Acting Insulin on Post-Prandial Hyperglycemia

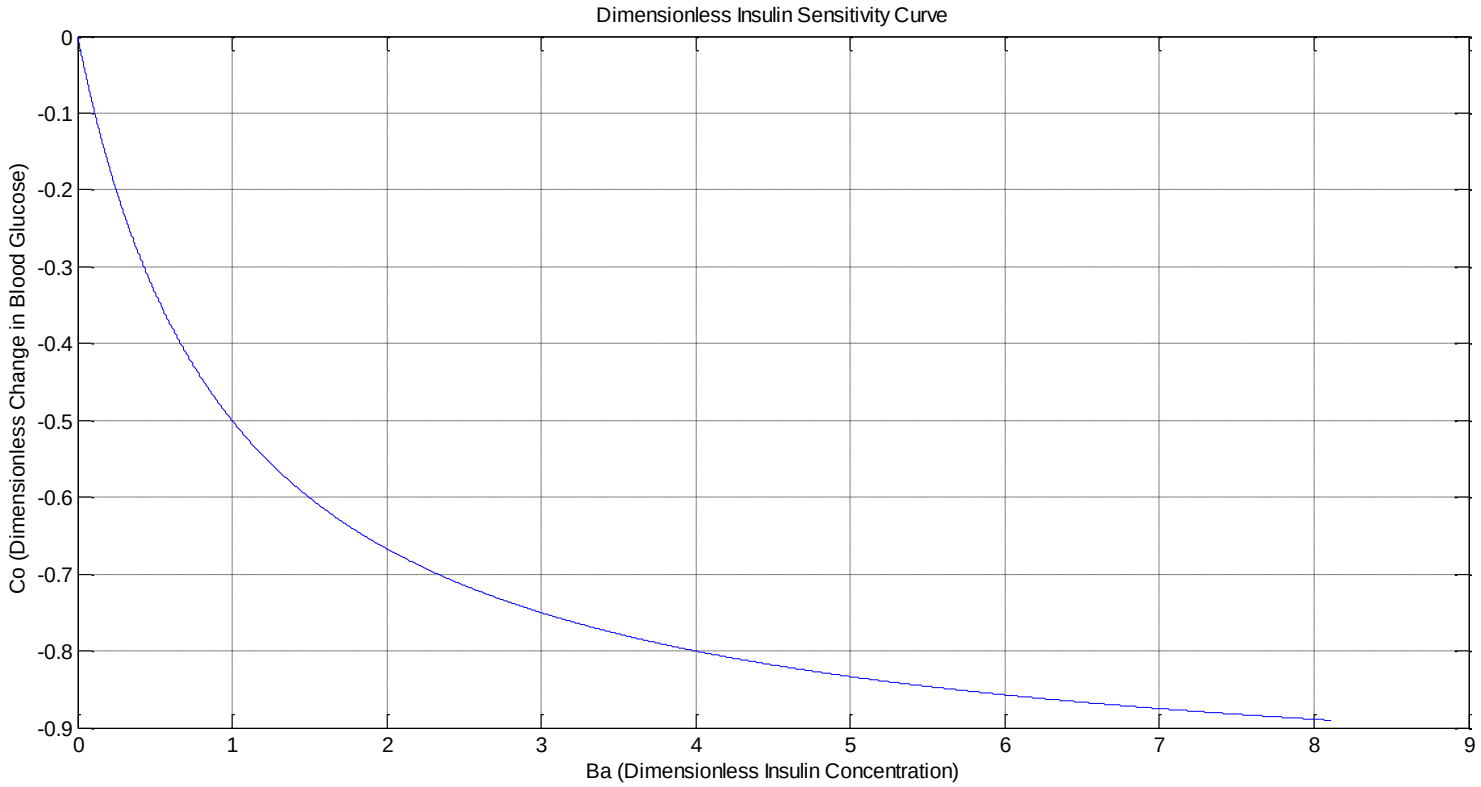

Figure 4-3: Dimensionless Insulin Therapy Curve

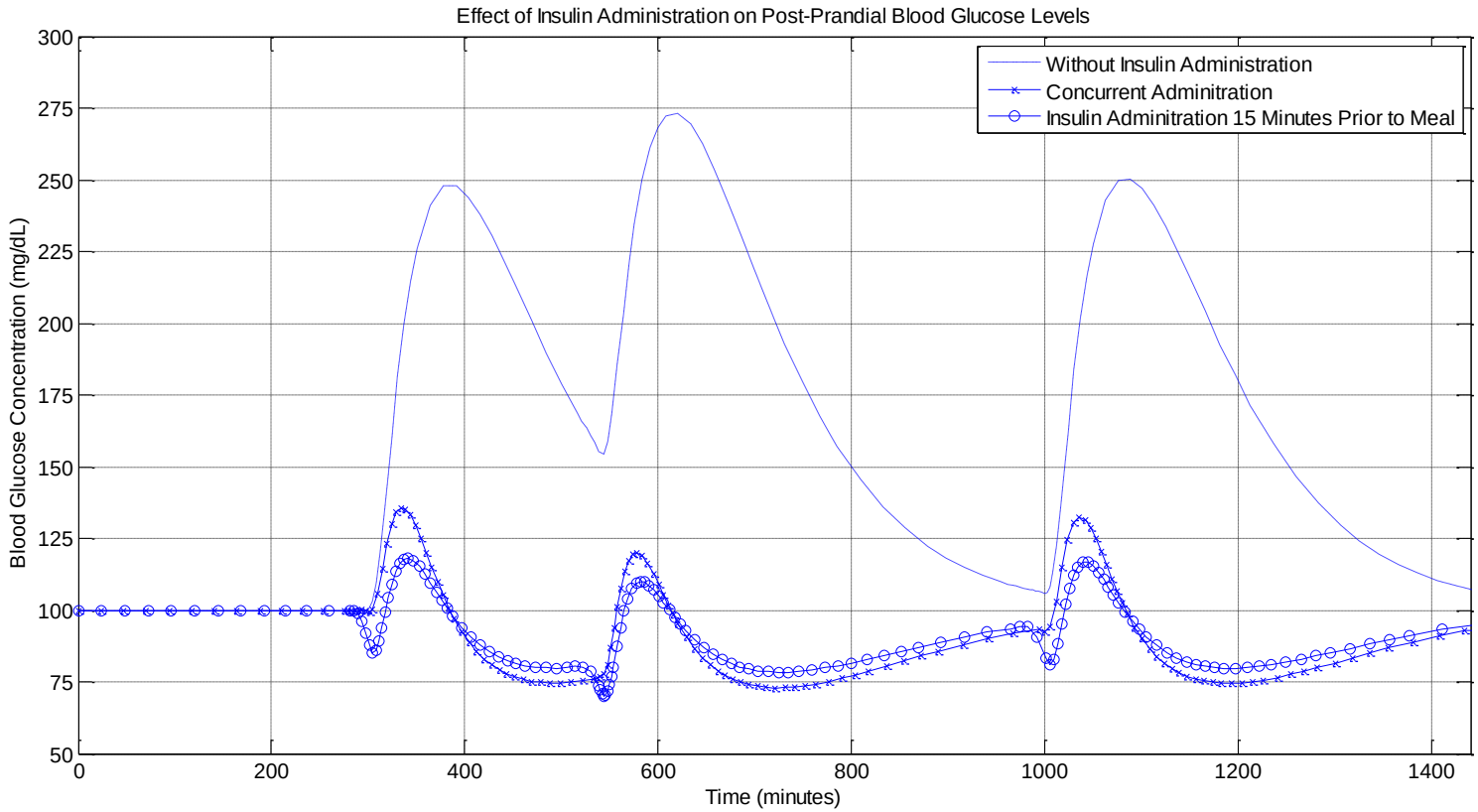

Figure 4-4: The Effect of Insulin Timing on Post-Prandial Glycemia

Parameter	Nominal Value	σ_{p_j}
p_1 *(min^{-1})*	1.57 x 10^{-2}	1.0 x 10^{-3}
G_b *(mg/dl)*	100	7.9
p_2 *(min^{-1})*	1.23 x 10^{-2}	4.3 x 10^{-4}
S_i *(L/min-U)*	5.0 x 10^{-1}	1.1 x 10^{-2}
k_e *(min^{-1})*	1.82 x 10^{-2}	5.2 x 10^{-4}
k_{abs} *(min^{-1})*	1.20 x 10^{-2}	3.8 x 10^{-4}
k_{emp} *(min^{-1})*	1.80 x 10^{-1}	1.5 x 10^{-2}
V_i *(L)*	12	3.0 x 10^{-1}
$\frac{fk_{abs}}{V_G}$ *(mg/dL-min-gCHO)*	8.00 x 10^{-2}	2.0 x 10^{-3}
I_b *(U/L)*	4 x 10^{-2}	2.0 x 10^{-3}
ISF (mg/dL-U)	45	4.07
I2C (g-CHO/U)	52	5.4
$I_{d,basal}$ *(U)*	12.6	0.79

Table 4-1: Nominal Parameter Values and Their Uncertainties

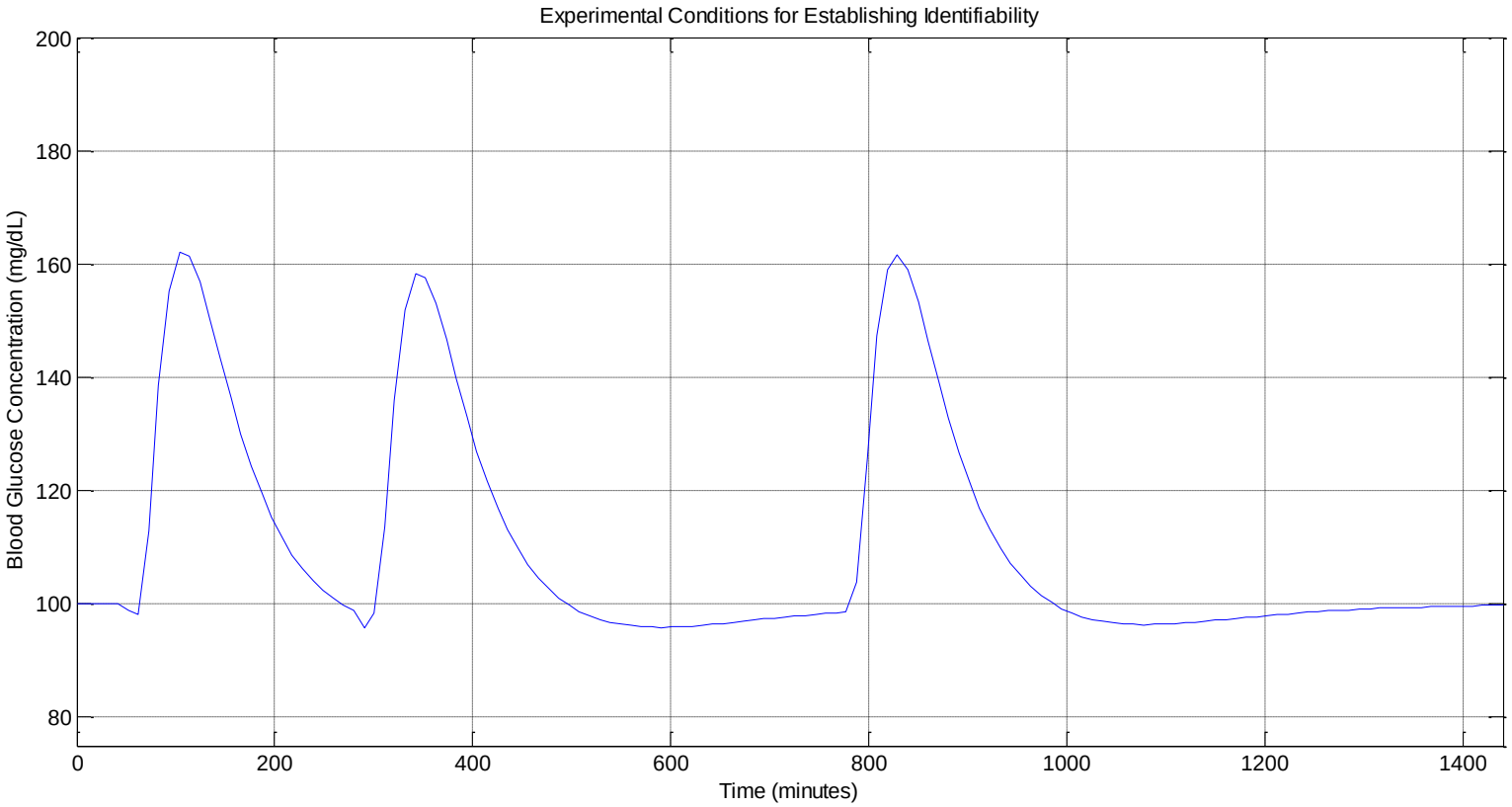

Figure 4-5: Identifiability of the Bergman Minimal Model

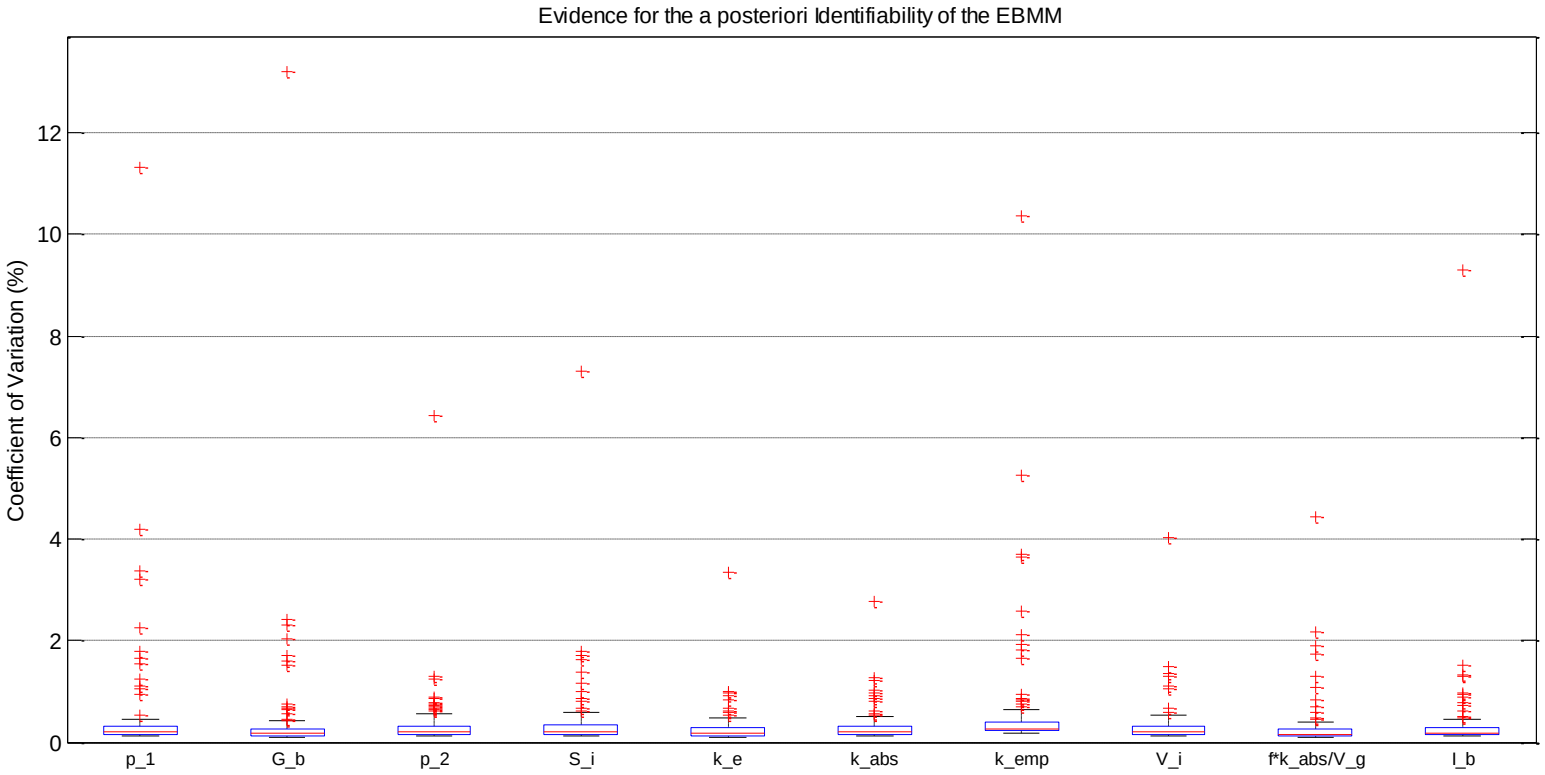

Figure 4-6: Identifiability of the EBMM across a range of parameters

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Chapter 5: Parameter Identification – Personalizing Insulin Therapy

Having developed a way to calculate clinical insulin therapy parameters, from the Extended Bergman Minimal Model, we now turn to the task of personalization through parameter estimation.

Having been in use for over 30 years, the Bergman Minimal Model has been the subject of numerous parameter estimation studies. Many focus on the model's original purpose, which was to provide an estimate of insulin sensitivity from a controlled clinical experiment [1], [2]. Collecting data from either an intravenous glucose tolerance test (IVGTT), many researchers have had the advantage of measuring both glucose and insulin concentrations over the course of their experiment [3], [4], [5]. However, as we seek to develop personalized insulin therapy that may be adapted under home-use conditions, we must consider the case where insulin measurements are unavailable.

METHODS

To assess whether parameter identification can take place under home-use conditions we propose two simple experimental scenarios. Test data is generated by creating two cohorts of patients based on the Extended Bergman Minimal Model and the more complicated Hovorka model. In addition, two 24-hour segments of real CGM data with accompanying meal and insulin logs are also used. Parameter estimation is then performed by fitting the Extended Bergman Minimal Model to the simulated or real data.

By attempting to fit the Extended Bergman Minimal Model to measurements generated by the Hovorka model, as well as real CGM measurements, we can assess whether the insulin therapy calculators derived in Chapter 4 are robust enough to work in a real clinical setting.

The Hovorka Model

The Hovorka Model of glucose-insulin dynamics is an eight compartment model, which encompasses three subsystems and includes three auxiliary equations. Originally developed using labeled IVGTT data, the model has since been used to implement nonlinear model predictive control in clinical trials of closed-loop insulin therapy [6], [7]. It is a compromise between the parsimony of the Bergman Minimal Model and the unwieldiness of larger more physiologically based models such as that of Sorensen [8].

Glucose Subsystem

The glucose subsystem is composed of two compartments, described by the differential equations in Equation 5.1 and Equation 5.2, as well as the three auxiliary equations show in Equations 5.3 – 5.5.

$$\frac{dQ_1}{dt} = \left(\frac{F_{01}^c}{V_G G} + x_1\right) Q_1 + k_{12} Q_2 - F_r + U_G + EGP_0(1 - x_3) \tag{5.1}$$

$$\frac{dQ_2}{dt} = x_1 Q_1 - (k_{12} + x_2) Q_2 \tag{5.2}$$

$$F_{01}^c = \begin{cases} F_{01}, & G \geq 4.5\ mmol/L \\ F_{01}\dfrac{G}{4.5}, & G < 4.5\ mmol/L \end{cases} \tag{5.3}$$

$$F_r = \begin{cases} 0.003(G - 9)V_g, & G \geq 9\ mmol/L \\ 0, & G < 9\ mmol/L \end{cases} \tag{5.4}$$

$$U_G = \frac{D_G A_G t e^{-\frac{t}{t_{max,G}}}}{t_{max,G}^2} \tag{5.5}$$

Equation 5.1 describes the total mass of glucose found in the accessible compartment—i.e., the blood and interstitium. The primary state variables include Q_1 and Q_2 which are the masses of glucose in the accessible and inaccessible compartments. Parameters include: the distribution volume of glucose V_G, the transfer coefficient between the glucose compartments k_{12} and the rate of endogenous glucose production at zero insulin concentration EGP_o.

The auxiliary terms are: the total insulin-independent rate of glucose consumption F_{01}^c, given by Equation 5.3, the rate of renal glucose clearance F_r given by Equation 5.4 and the rate of glucose absorption following a meal of size D_G given by Equation 5.5. Equation 5.5 is the equivalent the impulse response of a two-compartment model with identical transfer rates $1/t_{max,G}$. The final term in Equation 5.5 is A_G the bioavailability of carbohydrates in the meal.

Insulin Subsystem

The absorption and elimination of insulin following subcutaneous administration are governed by Equations 5.6 – 5.8.

$$\frac{dS_1}{dt} = u - \frac{S_1}{t_{max,I}} \tag{5.6}$$

$$\frac{dS_2}{dt} = \frac{S_1 - S_2}{t_{max,I}} \tag{5.7}$$

$$\frac{dI}{dt} = \frac{S_2}{V_I t_{max,I}} - k_e I \tag{5.8}$$

Equation 5.6 and Equation 5.7 model the transfer of insulin between two subcutaneous insulin compartments, S_1 and S_2, essentially acting as series low-pass filters between the insulin infusion rate u and the appearance of insulin in the plasma. As in the meal model of Equation 5.5, the transfer rates between the compartments, given by $1/t_{max,I}$, are identical.

Having passed through the subcutaneous compartments, the behavior of insulin in the plasma, state variable I, is governed by Equation 5.8. Parameters in Equation 5.8 include the distribution volume of insulin in the plasma V_I and the rate of insulin clearance k_e.

While the work of Hovorka *et al.* [6] is primarily concerned with continuous subcutaneous insulin infusion—i.e., insulin pumping—we use this subsystem in conjunction with Equation 4.5 and Equation 4.6 when modeling subcutaneous insulin injections.

Insulin Action Subsystem

Finally, the pharmacodynamic action of insulin is governed by the three compartments of Equations 5.9 – 5.11.

$$\frac{dx_1}{dt} = -k_{a1}x_1 + k_{b1}I \qquad 5.9$$

$$\frac{dx_2}{dt} = -k_{a2}x_2 + k_{b2}I \qquad 5.10$$

$$\frac{dx_3}{dt} = -k_{a3}x_3 + k_{b3}I \qquad 5.11$$

State variables are x_1, x_2 and x_3, which model the effect of insulin on glucose clearance in compartments Q_1 and Q_2 as well as endogenous glucose production. A total of six activation and deactivation constants are given by k_{ai}, $i = 1, 2, 3$, and k_{bi}, $i = 1, 2, 3$.

Generating Test Data

Two cohorts of virtual patients were generated from the models of Bergman and Hovorka. To generate a patient, the nominal parameter vector from the model was taken and each entry was multiplied by a random number, uniformly drawn from between 0.7 and 1.3. This was repeated 150 times for the nominal parameters of the Bergman model and 30 times for the Hovorka model. This method is equivalent to saying that for a given patient, each parameter is a random vector whose elements are uniformly distributed within +/- 30% of their expected or nominal value. The nominal parameter values for the Bergman and Hovorka models are contained in Table 5-1 and Table 5-2.

To give an example as to how realistic these virtual patients are, the ISF, I2C and ideal basal dose for both Bergman and Hovorka patients are presented in Figures 5-1 – 5-3. For the Bergman model, these were calculated directly from the model parameters. For the Hovorka model, these were determined by numerical simulation.

To numerically calculate ISF, I2C and the ideal basal dose, each Hovorka patient was first given a 10 U dose of once daily long-acting insulin in the absence of any other insulin or meal inputs. The basal dose was titrated in increments of 0.25 U until the patient reached a stable blood glucose concentration of between 90 mg/dL and 110 mg/dL. Having achieved fasting euglycemia, the ISF was determined by measuring the maximum drop caused by the administration of 1 U of rapid-acting insulin. The I2C was then calculated by challenging the patient with a 50 g-CHO meal and 5 U of co-administered rapid-acting insulin. The insulin dose was titrated in increments of 0.25 U

until post-prandial glycemia was kept between a maximum of 160 mg/dL and a minimum of 80 mg/dL.

In addition to simulated data, two 24-hour episodes of human CGM measurements from a single individual with T1DM were also used for model identification. These CGM measurements were collected as part of a study conducted by Abbott Diabetes Care to evaluate the FreeStyle Navigator under home-use conditions. The two blood glucose traces, as well as the accompanying meal and insulin logs are presented below Figures 5-4 – 5-5 and Tables 5-3 and 5-4.

Experimental Design

Two experimental scenarios were considered for both the Bergman and Hovorka cohorts.

In Scenario 1, each subject was injected with an ideal dose of long-acting insulin at t=0 and was subsequently provided with 50 g-CHO and 1 U of rapid-acting insulin at t=120 minutes. Blood glucose measurements were recorded for a total of 720 minutes.

In Scenario 2, each subject was injected with an ideal dose of long-acting insulin at t=0 and was subsequently provided with 50 g-CHO and 2 U of rapid-acting insulin at t=120 minutes, 70 g-CHO and 3 U of rapid-acting insulin at t=420 minutes as well as 30 g-CHO and 1 U of rapid-acting insulin at t=660 minutes. Blood glucose measurements were recorded over a total of 1440 minutes.

To examine the significance of measurement frequency, sampling times of 1-minute and 10-minutes were considered for both Scenario 1 and Scenario 2.

To examine the significance of measurement noise, a noisy sample was created by adding Gaussian noise of mean zero and standard deviation 10 mg/dL to the 10-minute sampling in Scenario 2.

Finally, three different meal/insulin log errors were considered using noise-free data from Scenario 2 with a 10-minute sampling frequency. For Error 1, the time-stamp on the first meal and insulin inputs was falsely recorded as t=90 minutes. For Error 2, the recorded insulin amount was set to 0 for the second meal to simulate a log omission. Finally, for Error 3, the last meal is falsely recorded as having been 45 g-CHO to simulate incorrect estimation.

Optimization

As mentioned before, we wish to fit the parameters of the EBMM to our data so that we can estimate the ISF, I2C and ideal basal insulin dose of our patients.

Typically, parameter estimation consists of minimizing the sum of squared errors, as in Equation 3.5, or another suitable objective function, between a set of reference data and a parameterized model. While this approach works well for a wide variety of problems, parameter estimation in dynamic systems, such as the Bergman Minimal Model, is generally ill-conditioned and numerically unstable [9]. Because of this numerical instability and the computational cost associated with numerical integration, parameter estimation can be difficult. As evidence, the standard approach of minimizing the sum of squared errors of the blood glucose measurements, produced no acceptable results when fitting the Bergman Minimal Model to data simulated using the Hovorka model or to the real CGM measurements shown in Figure 5-4 and Figure 5-5.

To remedy this problem, a technique known as principal differential analysis (PDA) was utilized. The procedure is described in Chapter 3, but briefly, splines were fit to our simulated data and used to calculate the derivative of the data at each time point t_m. Then Equation 4.1 was used to calculate the derivative of the Bergman Minimal Model at the same time points. To do this, the measured glucose was substituted in for G and the

meal and insulin logs were used to calculate X and G_{gut}. The error between the derivative of the measurements and the derivative calculated by the model was minimized in MATLAB 2010b using lsqnonlin. The optimization routine was initialized using the parameter values in Table 5-1 and the routine was provided with a lower bound of zero for each parameter and an upper bound of 1.8 times the nominal value.

RESULTS AND DISCUSSION

Below we summarize and discuss the results for parameter estimation using both simulated and real CGM data.

Parameter Estimation in the Bergman Cohort

Performing parameter estimation of the EBMM by using measurements simulated with the same model serves as a litmus test for the feasibility of our approach. If parameter estimation was unsuccessful in the absence of any model mismatch, it could hardly be expected to succeed when looking at either a different model structure or actual human data.

Fortunately, estimation of the parameters was completed successfully and a representative fit can be seen in Figure 5-6. Looking at Table 5-5 we see that for each of the two scenarios and two sampling frequencies that, in the absence of noise, estimates of the ISF are fairly unbiased and have a standard deviation of around 10%. The same is true for I2C with the exception of the 10-minute sampling of Scenario 2 with an average underestimation of 6.4%. Similarly, we see that the ideal basal dose is estimated with nearly zero bias and a standard deviation of around 6%, except in the 10-minute sampling of Scenario 2 where a small overestimation of 2.4% was observed. These biases in the 10-minute sampling of Scenario 2 are assumed to be idiosyncratic, owing to numerical instability and not a fundamental result of the experimental protocol.

Recalling the identifiability results of Chapter 4, located in Table 4-1, these results are in line with the standard deviations estimated by the Fisher Information Matrix, which were 9.0% for the ISF, 10.4% for the I2C and 6.3% for the ideal basal dose.

For the noisy measurement stream, our estimates suffered as expected. The ISF and I2C showed an average underestimation of 4.3% and 15% respectively, while the ideal basal dose was overestimated by 7.2%. The spread of estimate error also increased with the ISF, I2C and ideal basal dose having standard deviations of 15.0%, 17.8% and 11.2% respectively.

Finally, to provide a summary statistic for the goodness of fit, the mean amplitude of relative deviation was calculated for each fit. The average MARD is reported in Table 5-5 and for each noise-free measurement set was less than 1% increasing to 5.5% for the noisy measurement set.

Considering estimation given errors in the meal/insulin log, we see that while estimates did worsen in general the effect of noisy CGM measurements was more significant than the errors that were considered. A summary of these results can be found in Table 5-6.

Parameter Estimation in the Hovorka Cohort

Parameter estimation in the Hovorka Cohort was as expected more difficult. One of the best fits is shown in Figure 5-7 and while certainly adequate, with an MARD of around 9%, in general the EBMM struggled to capture the full dynamic range of the Hovorka Cohort.

However, despite this, both ISF and I2C were estimated successfully. On average, estimates of the ISF have only a small negative bias and again have a standard

deviation of around 6% for all noise-free measurements sets. Estimates of I2C suffer somewhat having a small negative bias of around 5% and a standard deviation of around 10% as was the case with the Bergman Cohort. However, estimates of the ideal basal dose are extremely poor, being consistently overestimated by a factor of 1.5. The consistency of this overestimation is due to the one or more of the constraints in the optimization routine being active.

The addition of noise has a smaller effect on parameter estimation in the Hovorka Cohort than in the Bergman Cohort. The reason for this is unknown, but it is speculated that because the dynamic correspondence between the models was poor, as evidenced by an average MARD of between 20% and 28% for all scenarios, the addition of 10% Gaussian noise was not as impactful.

As with the Bergman Cohort, time stamp errors and event magnitude errors had a minor impact on parameter estimation. However, the omissions of log data caused significant underestimation of both the ISF and I2C.

Data for overall estimation and estimation in the presence of log errors is presented in Table 5-7 and Table 5-8.

Parameter Estimation from Real CGM Data

The ability of the Bergman Minimal Model to fit real CGM data is shown in Figure 5-8. The model errors are confined to within +/- 50 mg/dL and are nearly zero mean. In addition, ISF, I2C and ideal basal dose were estimated as 18.28 mg/dL-U, 2.74 g-CHO/U and 40 U.

While unlike in the case of a synthetic patient, we cannot determine this individual's true ISF as we can with virtual patients, we can estimate it using the so-called Rule of 1800, which states that a person's insulin sensitivity factor is

approximately equal to 1800 divided by their total daily dose of insulin. The relevant meal/insulin log for this fit is contained in Table 5-3 and indicates that on the day in question this person's total daily dose was 95 U, including both rapid-acting and long-acting insulin, implying an ISF of 18.95 mg/dL-U. Further, we can see from inspecting Table 5-3 that this person was using between 3.33 U and 3.75 U of insulin for each carbohydrate they consumed. Lastly, the person uses a total of 50 U of long-acting insulin split between the morning and early evening.

This result allows for two possible interpretations. First, it is possible that this person is already receiving their ideal therapy and that discrepancy between the estimated and observed insulin-to-carbohydrate ratio and basal dose is a result of parameter underestimation. Alternatively, one can interpret this to say that our insulin therapy framework is recommending that this individual should decrease their basal dose by 10 U and increase their meal-time insulin by about 30%.

Regardless, successful parameter estimation given real CGM data was no mean feat. Unlike parameter estimation in the Bergman and Hovorka cohorts, which was performed using a single initial parameter guess, dozens of initial parameter guesses were considered before the result shown in Figure 5-8 was reached. Further, parameter estimation given the second segment of CGM data was not successful.

SUMMARY AND CONCLUSIONS

Parameter estimation of the Bergman Minimal Model under home-use conditions was performed for two cohorts of virtual patients, one generated from the Extended Bergman Minimal Model itself and the over generated using the Hovorka model. In addition, parameter estimation was also performed using two segments of real CGM data.

For the cohort of patients simulated using the Bergman Minimal Model, good estimates for the ISF, I2C and basal insulin dose were found in the absence of noise or meal/insulin log errors. The addition of noise or log errors decreased the quality of parameter estimates and increased their distribution, but the results were still acceptable.

Similar results were obtained for the Hovorka Cohort, with the exception that the basal dose was very poorly estimated and that omission errors in the log caused a significant degradation in parameter estimation. Promisingly, while the presence of measurement noise caused a slight underestimation in the ISF and I2C, their variance was not significantly inflated as with the Bergman Cohort.

Finally, successful parameter estimation was possible for only one of the two segments of real CGM data and only then after a significant effort was expended. However, estimates of the ISF, I2C and basal insulin dose calculated from equations of Chapter 4 are in good agreement with those inferred from the individual's recorded log.

Given these results, it appears that using CGM data collected under home-use conditions it is possible to directly identify person-specific values for the insulin sensitivity factor, insulin-to-carbohydrate ratio and basal insulin dose with both accuracy and precision.

Parameter	Nominal Value
$p_1\ (min^{-1})$	1.57×10^{-2}
$G_b\ (mg/dl)$	100
$p_2\ (min^{-1})$	1.23×10^{-2}
$S_i\ (L/min\text{-}U)$	5.0×10^{-1}
$k_e\ (min^{-1})$	1.82×10^{-2}
$k_{abs}\ (min^{-1})$	1.20×10^{-2}
$k_{emp}\ (min^{-1})$	1.80×10^{-1}
$V_i\ (L)$	12
$Vg\ (L)$	12
$I_b\ (U/L)$	4×10^{-2}

Table 5-1: Nominal Parameters for the Bergman Model

Parameter	Nominal Value
k_{12} *(min^{-1})*	6.6×10^{-2}
k_{a1} *(min^{-1})*	6.0×10^{-3}
k_{a2} *(min^{-1})*	6.0×10^{-2}
k_{a3} *(min^{-1})*	3.0×10^{-2}
k_e *(min^{-1})*	1.38×10^{-1}
V_i *(L/kg)*	1.2×10^{-1}
Vg (L/kg)	1.6×10^{-1}
A_g	8.0×10^{-1}
$T_{max,g}$ *(min)*	40
$T_{max,i}$ *(min)*	55
S_{IT} *(mU/L-min)*	5.12×10^{-3}
S_{ID} *(mU/L-min)*	8.2×10^{-4}
S_{IE} *(mU/L-min)*	5.2×10^{-2}
EGP_o *(mmol/kg-min)*	1.61×10^{-2}
F_{01} *(mmol/kg-min)*	9.7×10^{-3}
Weight (kg)	78
Median Basal Insulin Dose (U)	8.5
Median ISF (mg/dL-U)	46
Median I2C (g-CHO/U)	25

Table 5-2: Nominal Parameters for the Hovorka Model

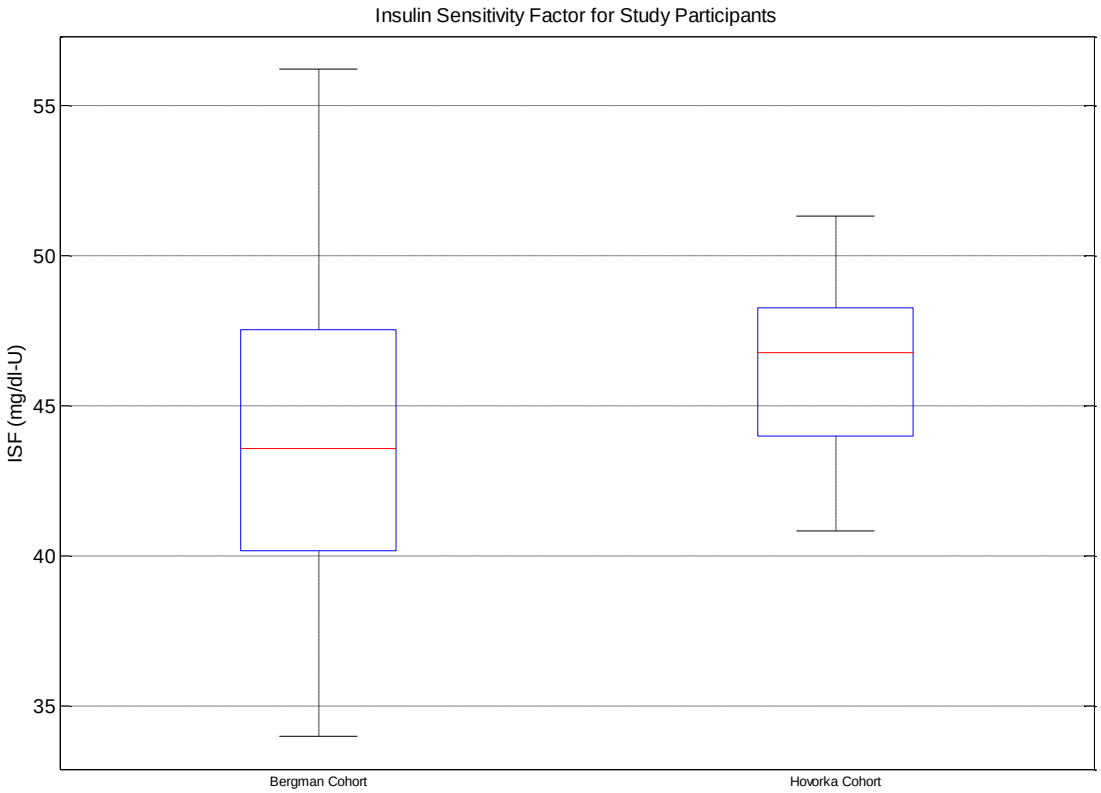

Figure 5-1: Insulin Sensitivity Factor of Synthetic Patients

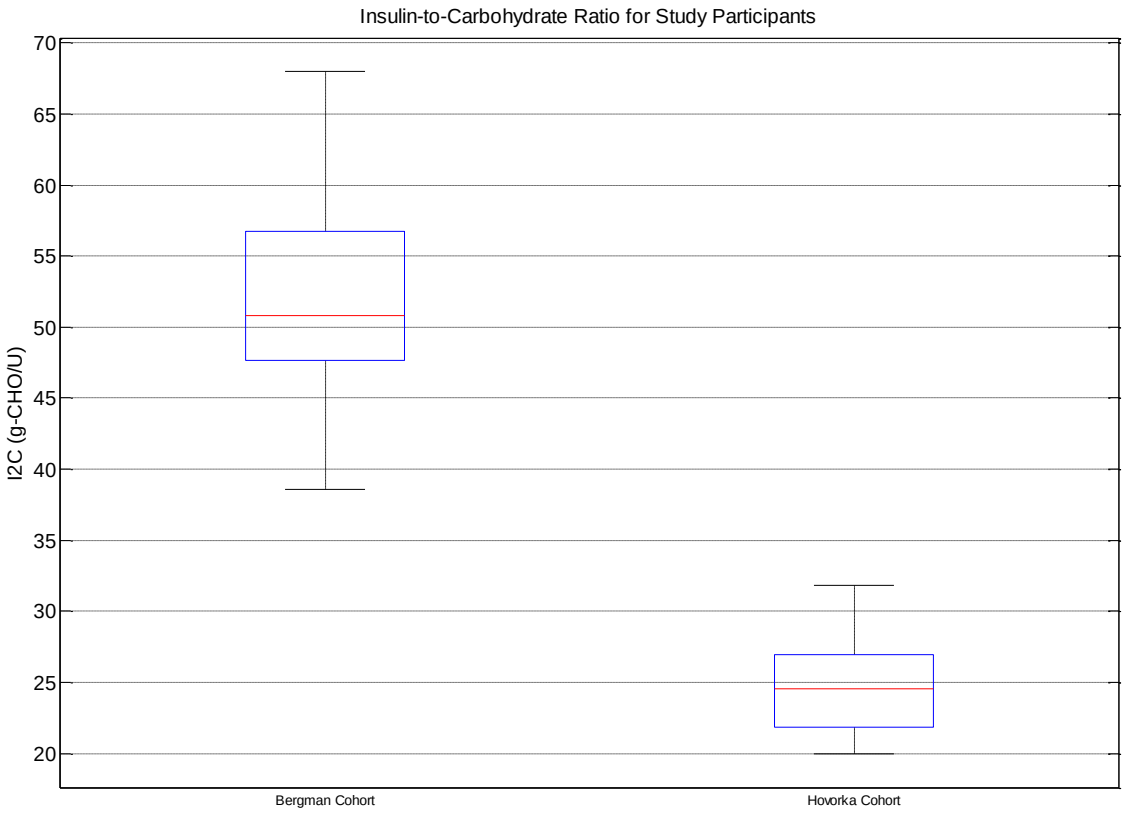

Figure 5-2: Insulin-to-Carbohydrate Ratios of Synthetic Patients

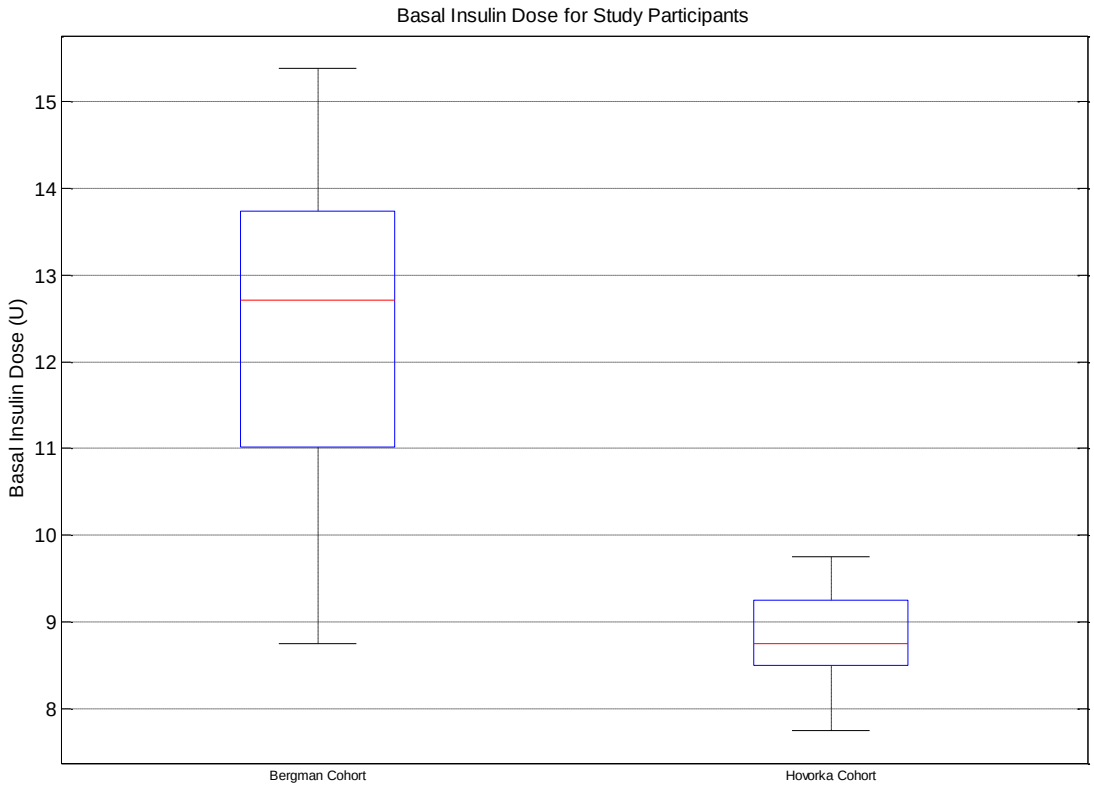

Figure 5-3: Basal Insulin Requirements of Synthetic Patients

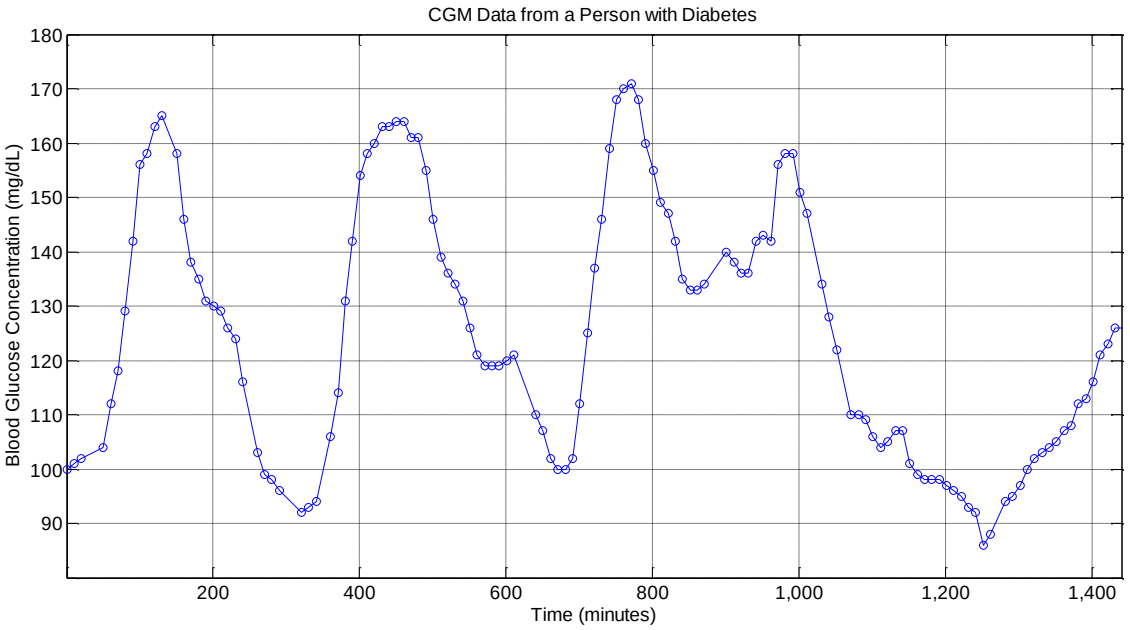

Figure 5-4: Real CGM Measurements: Segment One

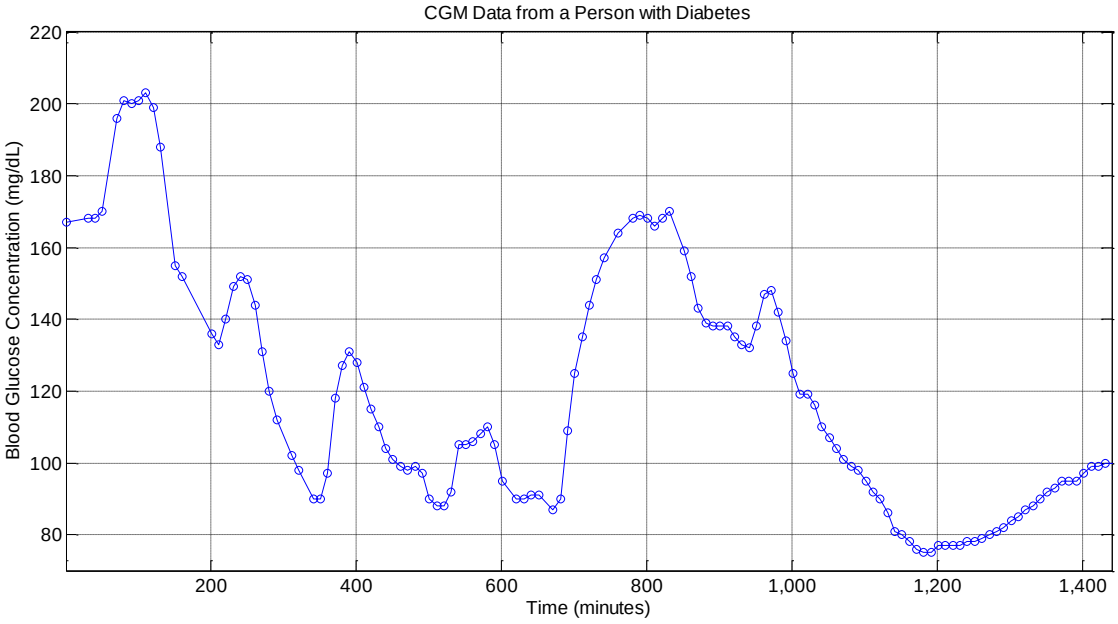

Figure 5-5: Real CGM Measurements: Segment Two

Event Type	Event Size	Event Time (minutes)
Insulin: Long-acting	25 U	41
Insulin: Rapid-acting	12 U	41
Meal	45 g-CHO	42
Insulin: Rapid-acting	12 U	310
Meal	45 g-CHO	310
Insulin: Rapid-acting	12 U	632
Meal	45 g-CHO	632
Insulin: Rapid-acting	9 U	890
Meal	30 g-CHO	891
Insulin: Long-acting	25 U	891

Table 5-3: Meal and Insulin Log for a Person with Diabetes

Event Type	Event Size	Event Time
Insulin: Long-acting	25 U	20
Insulin: Rapid-acting	25 U	20
Insulin: Rapid-acting	14 U	20
Meal	45 g-CHO	20
Insulin: Rapid-acting	12 U	309
Meal	45 g-CHO	310
Insulin: Rapid-acting	20 U	331
Meal	75 g-CHO	333
Meal	45 g-CHO	620
Insulin: Long-acting	12 U	662
Meal	30 g-CHO	846
Insulin: Rapid-acting	10 U	846
Insulin: Long-acting	25 U	847

Table 5-4: Meal and Insulin Log for a Person with Diabetes

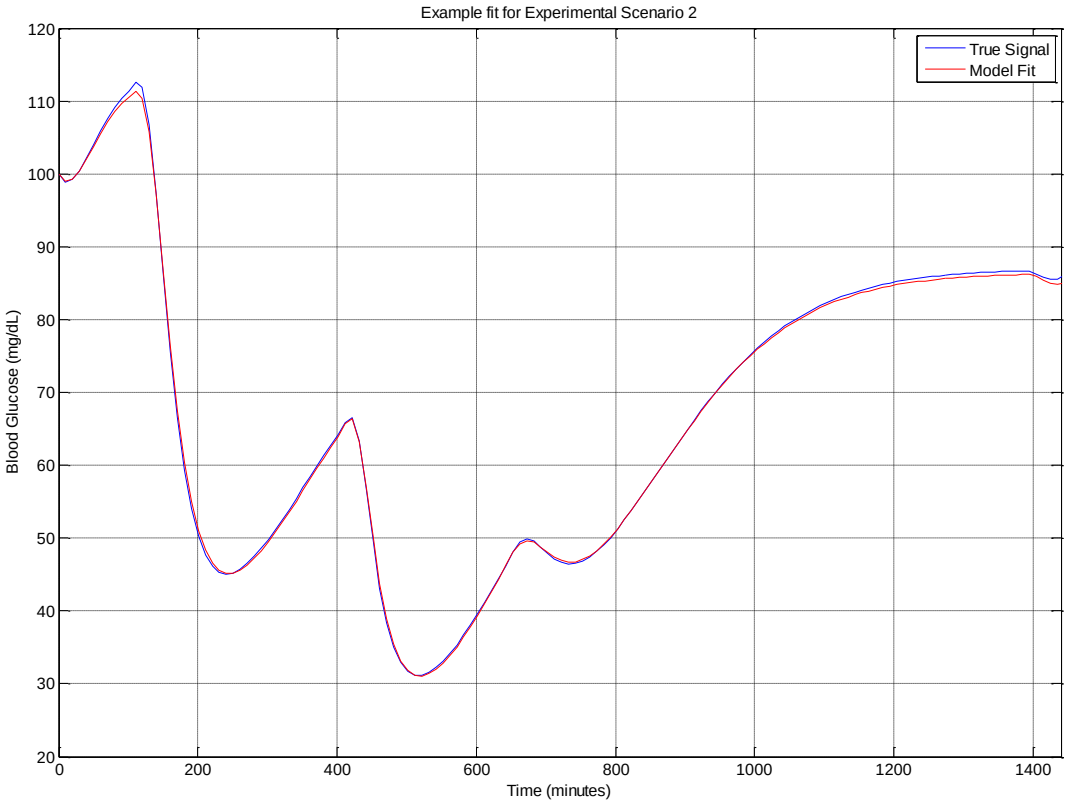

Figure 5-6: Model fit in the Bergman Cohort

	Scenario 1 (1-minute)	Scenario 1 (10-minute)	Scenario 2 (1-minute)	Scenario 2 (10-minute)	Scenario 2 (Noisy)
ΔISF (%)	0.8 ± 9.4	1.7 ± 12.0	0.3 ± 10.4	0.6 ± 11.0	-4.3 ± 15.0
ΔI2C (%)	1.6 ± 9.9	0.2 ± 9.7	0.7 ± 9.9	-6.4 ± 9.7	-15.0 ± 17.8
ΔBasal (%)	0.5 ± 6.0	-0.03 ± 5.9	0.43 ± 4.8	2.6 ± 6.0	7.2 ± 11.2
MARD (%)	0.2	0.8	0.47	0.9	5.5

Table 5-5: Parameter Estimation in the Bergman Cohort

	Log Error 1 (Time Stamp)	Log Error 2 (Log Omission)	Log Error 3 (Event Magnitude)
ΔISF (%)	-1.9 ± 11.8	-0.08 ± 12.2	-2.4 ± 1.2
ΔI2C (%)	-11.4 ± 14.1	-0.2 ± 15.9	-6.7 ± 14.6
ΔBasal (%)	2.6 ± 8.7	0.8 ± 6.9	2.1 ± 6.3
MARD (%)	2.5	1.1	1.3

Table 5-6: Parameter Estimation in the Bergman Cohort with Log Errors

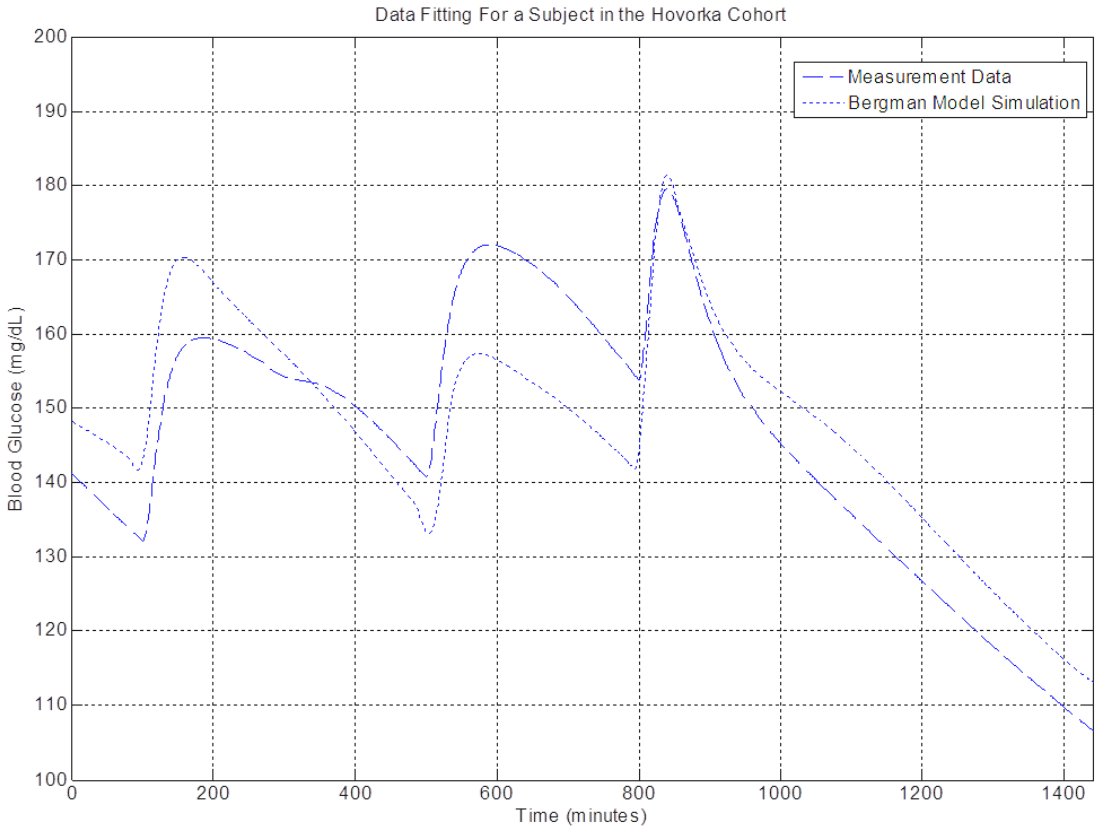

Figure 5-7: Model fit in the Hovorka Cohort

	Scenario 1 (1-minute)	Scenario 1 (10-minute)	Scenario 2 (1-minute)	Scenario 2 (10-minute)	Scenario 2 (Noisy)
ΔISF (%)	-1.0 ± 6.0	-0.8 ± 6.1	-3.5 ± 6.6	0.2 ± 6.0	-4.0 ± 6.8
ΔI2C (%)	-5.0 ± 10.0	-4.7 ± 10.1	-7.5 ± 9.3	-4.9 ± 9.3	-6.9 ± 9.4
ΔBasal (%)	154.3 ± 14.8	154.3 ± 14.8	154.0 ± 15.1	151.0 ± 18.2	154.0 ± 14.8
MARD (%)	20.6	20.5	27.0	28.5	28.6

Table 5-7: Parameter Estimation in the Hovorka Cohort

	Log Error 1 (Time Stamp)	Log Error 2 (Log Omission)	Log Error 3 (Event Magnitude)
ΔISF (%)	-0.6 ± 6.9	-12.0 ± 6.0	0.07 ± 6.0
ΔI2C (%)	-4.7 ± 9.4	-15.6 ± 8.2	-5.0 ± 9.3
ΔBasal (%)	154.3 ± 14.8	151.0 ± 18.2	151.0 ± 18.3
MARD (%)	29.1	32.9	28.6

Table 5-8: Parameter Estimation in the Hovorka Cohort with Log Errors

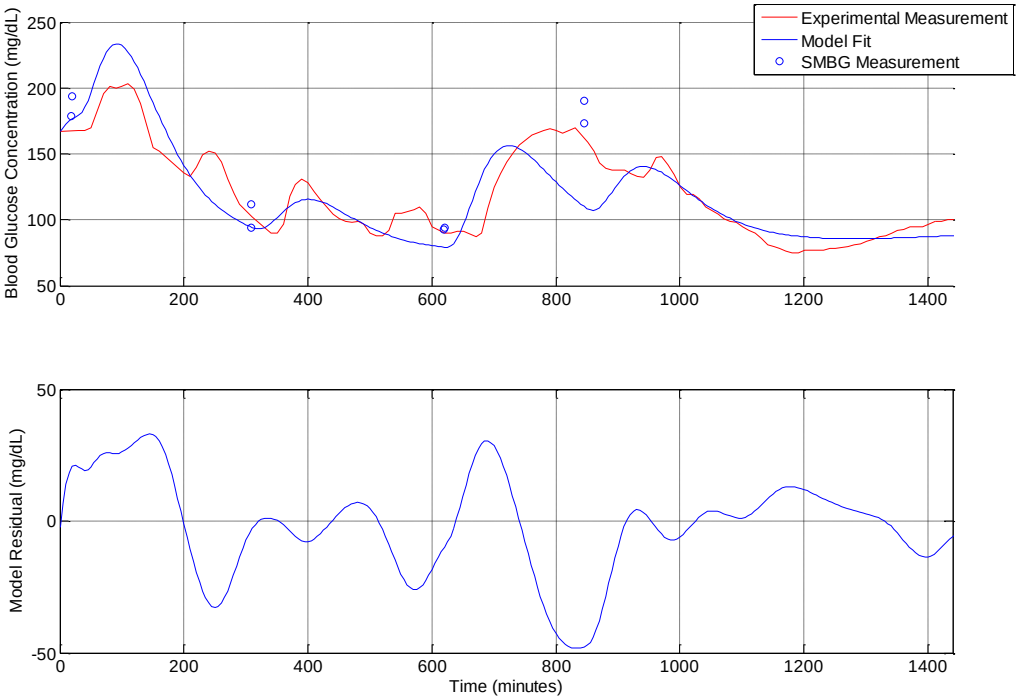

Figure 5-8: Fit of the Bergman Minimal Model to Real CGM Data

	Estimated from Bergman Minimal Model	Inferred from Meal/Insulin Log
ISF (mg/dL-U)	18.28	18.94
I2C (g-CHO/U)	2.74	3.54
Basal Dose (U)	40	50

Table 5-9: Estimated and Inferred Treatment Parameters for Real Data

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Chapter 6: The Physiology of Continuous Glucose Monitoring

The development of continuous glucose monitoring (CGM) has created a number of opportunities for improving the treatment and management of T1DM. For example, prior to the development of CGM, the implementation of ambulatory closed-loop insulin control was infeasible. Using CGM, numerous researchers are pursuing closed-loop insulin control [1], [2], some even envisioning a future where CGM-based meal detection makes the entire process of insulin delivery self-managing [3]. In addition, the ability to provide immediate feedback on how life choices affect glycemia is widely recognized as beneficial and has been shown to lower A1C absent any other intervention [4], [5], [6].

However, several factors currently limit the utility of CGM. Among these limitations are the accuracy and precision of measurements, issues with calibration, cost, limitations on FDA approved uses, reimbursement and education [1], [6], [7]. In addition, there are many anecdotal reports indicating that sensors tend to underestimate blood glucose at night or when a user lays heavily on the device.[1]

Numerous studies have evaluated the accuracy and performance of CGM devices; however, none of these authors have approached CGM device performance from a physiological basis. In this chapter, we propose a physiological model of the CGM environment. This model is used to analyze how different calibration schemes can affect the accuracy and precision of measurements derived from CGM. In addition, by considering the underlying physiology, we are able to demonstrate the potential causes for some of the technology's performance limitations.

[1] In fairness, given that complaints tend to arise from night-time alarms resulting from false lows it is entirely possible that these anecdotes are the result of an easily remembered annoyance and not a failure of CGM technology.

CONTINUOUS GLUCOSE MONITORING IN THE SKIN

When discussing CGM, we are most concerned with the subcutaneous layer of the skin. The subcutis or subcutaneous layer is between 10 – 15 mm in thickness and is located between 1.2 – 3.8 mm beneath the skin's surface; it is here that the probe of a CGM device is intended to analyze glucose content [8]. In the subcutis, capillary glucose is transported by convection and diffusion out of the capillaries and into the interstitial compartment—the extracellular environment in which the capillaries and other vessels are contained. Small lymphatic vessels permeate the interstitial space, much like the capillaries, allowing excess fluid and protein seepage from the capillaries to be removed. Because CGM devices actually measure interstitial glucose and not blood glucose, their performance will depend on the dynamic interplay of glucose transport between the capillaries, the interstitial compartment and the lymphatics.

MODELING INTERSTITIAL GLUCOSE DYNAMICS

Previous authors, when they have described the physical environment of the CGM device, have consistently omitted any mention of the lymphatics. However, researchers who study drug and solute disposition in skin have identified the singular importance of the role played by the lymphatics [9].

As such, we propose the following lumped model governing the disposition of glucose between the blood, interstitial compartment and lymphatics:

$$\left(\frac{dV_I G_I}{dt}\right) = P_{cap}S_{cap}\,(G_B - G_I) + P_{lym}S_{lym}\,(G_L - G_I) + Q\,\frac{(G_b + G_I)}{2} - QG_I - k_I G_I, \tag{6.1}$$

$$\left(\frac{dV_L G_L}{dt}\right) = Q\,(G_I - G_L) + P_{lym}S_{lym}\,(G_I - G_L) - k_L G_L. \tag{6.2}$$

Terms in Equation 6.1 include: G_B, G_I and G_L the concentrations of glucose in the blood, interstitium and lymphatics; V_I and V_L the volumes of the interstitial and lymphatic compartments; P_{cap} and P_{lym} the permeabilities of the capillary and lymphatic vessels; S_{cap} and S_{lym} the available surface area for transport across the capillary and lymphatic membranes; k_I and k_L the rate of glucose consumption in the interstitial and lymphatic compartments; and Q the rate of convective fluid flow from the capillaries into the interstitial compartment.

IDENTIFYING SOURCES OF UNCERTAINTY IN CONTINUOUS GLUCOSE MONITORING

A large body of work exists quantifying the accuracy and precision of CGM devices [10]–[13]. However, most work done on calibration is proprietary as it is of the greatest interest to manufacturers [14]–[16]. Further, while it is known that there is a lag or time delay between CGM measurements and the true blood glucose concentration, this particular problem has been primarily studied using empirical models in an attempt to quantify the lag and its effect on performance [17]–[19].

Below, we examine both one-point and two-point calibration schemes using the physiological model presented in Equations 6.1 and 6.2. While CGM manufacturers all have proprietary calibration procedures that no doubt take into account factors such as drift, variance in manufacturing and commonly observed error patterns, it is hoped that this analysis will still prove informative.

Calibration

Because CGM devices measure the concentration of glucose in the interstitial compartment and not in the blood, a glucometer is needed to calibrate the device. In

addition to an initial calibration, follow-on calibration is required at least every other day with some manufacturers recommending twice daily calibration.

Ignoring the issue of sensor drift, we sought to explore whether one-point or two-point initial calibration was superior. To evaluate this we used Equation 6.1 and Equation 6.2 along with the EBMM discussed extensively in Chapter 4. First, a blood glucose trace was simulated using the EBMM for two different sets of meal and insulin inputs. Equations 6.1 and 6.2 were then numerically integrated in MATLAB 2010b with ode45 using the previously simulated blood glucose trace as an input to Equation 6.1. The specific parameters used in Equation 6.1 and 6.2 are shown in Table 6-1. Figure 6-1 shows a trace of blood glucose concentration and the uncalibrated interstitial glucose concentration for one of the two simulated cases.

Calibration of the interstitial signal was then performed as follows. For single-point calibration a time-point was selected and the calibration factor (*CF*) was given by:

$$CF = \frac{G_B(t_{cal})}{G_I(t_{cal})}, \tag{6.3}$$

where G_b is the blood glucose concentration, G_I is the interstitial glucose concentration and t_{cal} is the time the calibration was performed. The calibrated blood glucose value was calculated by multiplying each interstitial blood glucose value by *CF*.

For two-point calibration, a simple linear model was selected. The parameters in the linear model were selected to satisfy the equation:

$$G_B(t_{cal}) = aG_I(t_{cal}) + b. \tag{6.4}$$

Each pair of calibration measurements specifies a fully-determined linear system given Equation 6.4. Solving this system for a and b, we then found the calibrated blood glucose value by substituting into Equation 6.4.

Calibration was performed only when the rate of change of blood glucose concentration was close to zero. In addition, two-point calibration was only performed at consecutive extrema that were separated by at least one hour. Example calibrations are shown in Figures 6.3 – 6.5.

To evaluate these calibrations, we used the mean absolute relative deviation (MARD), an industry standard used to evaluate CGM performance. MARD is calculated by taking the difference between a set of calibrated measurements and reference measurements, dividing each difference by the corresponding reference measurement and then taking the mean of the absolute value of these relative deviations.

Figure 6-3, which shows the results for three different single-point calibrations, is representative of the general performance of single-point calibration. The calibrations took place at 25 minutes (a minima), 80 minutes (during a time of rapid rise in the blood glucose concentration) and at 125 minutes (a maxima). The MARD for each of these three calibrations was found to be 8.4%, 7.0% and 11.4% respectively.

Considering the extra effort involved, one would hope that a two-point calibration would produce better results. In Figure 6-4, calibration measurements were taken at 50 minutes and 150 minutes for the "Minima-Maxima" calibration and at 25 minutes and 310 minutes for the "Minima-Minima" calibration. In Figure 6-5, calibration measurements were taken at 45 minutes and 125 minutes for the "Minima-Maxima" calibration and at 45 minutes and 175 minutes for the "Minima-Minima" calibration.

Examining Figures 6-4 and 6-5 we see that the extra effort does not always pay off. Specifically, it is possible to choose calibration times such that the system of

equations formed by Equation 6.4 is nearly singular. In this case, one can produce catastrophically bad calibrations as seen in the two "Minima-Maxima" calibrations. The MARDs for these two calibrations are 106.5% and 78.6% respectively.

To evaluate the issue of calibration more systematically, for each of the traces in Figure 6-4 and Figure 6-5, we performed all allowable calibrations as per the earlier defined rules and compared the results. In total, 21 one-point and 18 two-point calibrations were performed.

With respect to robustness, one-point calibrations are superior as the worst-case MARD was found to be 10.86% with the average MARD being 5.98%. By contrast, naïve two-point calibration is capable of spectacular failures as shown in Figure 6-4 and Figure 6-5. The worst-case MARD for two-point calibration was found to be 53.12% and the average MARD was found to be 21.35%. However, as mentioned before poor two-point calibration results from the creation of a nearly singular calibration system using Equation 6.4. If one restricts calibrations to those where a large change in blood glucose has taken place, the problem of singularity can be avoided. Considering only the two-point calibrations where blood glucose changed by at least 60 mg/dL between calibration points, the worst-case MARD decreases to 6.55% and the average MARD is 5.19%. In addition, MARD from two-point calibration is lower than the corresponding one-point calibration in all but two cases, with an average relative decrease of 4% and a median decrease of 3%.

Capillary Bed Perfusion

Assuming that manufacturers use one-point calibration in their meters, the above analysis helps to explain a MARD of around 6%. However, studies have shown that for CGM devices MARD can range between 14% - 20% depending on the manufacturer

[10], [13]. While some of this discrepancy can be explained by the absence of additive noise in our model, as well as the presence of manufacturing variability between lots [20], [21], we propose that variations in perfusion of the capillary bed are also significant.

In Equation 6.1 we modeled capillary perfusion as a constant S_{cap}. However, capillary perfusion is dependent on the perfusion of independent capillary vessels [22]. On average, the capillary bed is approximately 40% perfused, meaning that blood is actively flowing through only 40% of all available vessels [9]. However, during periods of exertion this can increase to 100% and during periods of inactivity this value will certainly decrease below the average [23]. To model this variability we choose to look at both random changes in perfusion, which may result from sudden movement or exertion, as well as diurnal variability in perfusion, which would arise from natural shifts in activity level over the day.

$$\hat{S}_{cap} = S_{cap}\left(0.4 + 0.1\sin\left(\frac{2\pi}{1440}t\right)\right) \quad 6.5$$

$$\hat{S}_{cap} = S_{cap}(0.4 + r) \quad 6.6$$

Equation 6.5 describes the case of diurnal variability and assumes that perfusion varies 25% about its mean in a sinusoidal fashion over a period of 24 hours.

Equation 6.6 describes the case of random variations to capillary perfusion. Here we only consider random increases to perfusion, modeling r as a uniformly distributed random number between 0 and 0.6.

To explore how this variability in capillary bed perfusion affects CGM performance, a 24-hour blood glucose trace was simulated using the EBMM as before

with the parameter S_{cap} in Equation 6.1 being modeled using Equation 6.5 or Equation 6.6. One-point calibration was performed 80 minutes into the simulation. For simplicity, two-point calibration was not performed. The results of these simulations are shown in Figures 6-6 – 6.8.

Considering first the case of diurnal variations in perfusion, we see from Figure 6-6 that this kind of variability can cause significant errors in CGM measurements. For the case of constant perfusion also shown in Figure 6-6, the MARD is 3.5%. By contrast, the MARD under the assumption of diurnal perfusion is 8.5%. Interestingly, the error in the calibrated CGM signal is actually lower for the case of diurnal variability leading up to around 7:00 pm in the evening. As a result, any follow-up glucometer readings are likely to lull the user into a sense of relative security. If the user were then to make a treatment decision later in the evening without first consulting a glucometer, the overestimation of blood glucose caused by the diurnal change in capillary perfusion would cause overtreatment and could induce hypoglycemia.

Turning our attention to Figure 6-7, we see that random diurnal variations in capillary perfusion could very easily be confused for additive measurement noise. While the noise appears to be zero mean, there is still an accompanying decrease in CGM performance with MARD increasing to 6.7%. An interesting feature that is also worth noting is the large decrease around 850 minutes. This error looks very much like a "drop-out" or attenuation event, which is a specific kind of CGM system fault that is familiar to those in the industry, but has not been widely discussed in the literature [24].

Finally, turning to Figure 6-8 the composition of diurnal and random variations is shown. While not qualitatively different from either of the preceding cases, CGM performance is further degraded with a MARD increasing to 10.4%. This suggests that

the errors introduced by diurnal variations and those induced by random variations in capillary bed perfusion may propagate additively or can at least be modeled as such.[2]

Externally Applied Pressure

Mentioned briefly in the preceding section, drop-outs are transient decreases in CGM measurement that produce a marked underestimation of blood glucose similar to the one shown in Figure 6-7. While not widely discussed in the literature, some drop-outs have been attributed to the application of external pressure at the CGM measurement site [24].

Looking at Equations 6.1 and 6.2 it is not obvious how pressure would explain the occurrence of these events. However, a deeper look at the physiology of the lymphatics provides some clue. The primary lymphatics, which collect fluid from the interstitial compartment, are connected to the surrounding tissues by filaments [25]. As the volume of the interstitial compartment expands, these filaments pull on the lymphatics allowing fluid to enter [25]. In the presence of an applied pressure, the lymphatic vessels would be held shut preventing fluid collection. To prevent local edema the body could respond by decreasing capillary perfusion, decreasing capillary permeability or by modulating local pressure fields which would reduce Q.

To simulate the effect of applied external pressure, we use the same blood glucose trace as shown in Figure 6-2, and induce a drop in Q to 20% of its nominal value at 600 minutes. This simulation is shown in Figure 6-8.

The effects of the applied pressure do not actually manifest themselves for over an hour despite a rapid decrease in the underlying blood glucose signal. However, once

[2] The root of the sum of the squared MARDs for the case of diurnal variations and the case of random variations to capillary bed perfusion is 10.81% which is close to the observed MARD for the composite case.

the blood glucose begins to rise rapidly at 680 minutes, the increased lag caused by the reduction in flow produces a drop-out of over 20 mg/dL. Subsequently, lower rates of change and then a large period of decreasing blood glucose allows the measurement signal to catch up with the true signal decreasing the apparent magnitude of the drop-out. However, another rapid rise in blood glucose would likely produce the same sort of underestimation observed at 680 minutes. While the delay between applied pressure and the observation of a drop-out does not agree with the observations of Baysal *et al.* [24], it is possible that there are multiple artifacts, each with a different cause, that have been lumped together as drop-outs or attenuation events.

SUMMARY AND CONCLUSIONS

We have shown that under some circumstances, two-point calibration of CGM devices is superior to one-point calibration by a relative 3% - 4%. However, two-point calibration requires that the calibration measurements be taken at times when the rate of change in blood glucose is small and that the difference in blood glucose concentration between the first and second measurement be large. If this second condition is not met, the calibration can fail catastrophically. One-point calibration by contrast only requires that the rate of change in blood glucose concentration be small. Therefore, we believe that one-point calibration should be the prevailing standard with optional two-point calibration occurring only when both conditions for adequate performance are satisfied.

In addition, our simulations suggest that CGM performance is limited as much by the underlying physiology of the interstitial compartment as by the chosen calibration method. Variations in capillary bed perfusion, arising from diurnal changes as well as random changes in activity level, increase MARD by 3.2% - 6.9%. While there is no immediate remedy to the issue at hand, this result suggests future directions for

improving CGM performance. For example, diurnal variations in capillary bed perfusion may very well depend on CGM insertion site. If a location on the body can be found where capillary bed perfusion is stable over time, diurnal variations in CGM error can be minimized. Further, minimizing the effect of random or unexpected changes in activity on CGM may be accomplished by combining activity data with CGM data. The rise of motion tracking devices, including the Lark (Lark Technologies, Mountain View, CA), Fitbit (Fitbit Inc., San Francisco, CA) and software-enabled smartphones provides an additional stream of information that could be used to build a more robust calibration model.

Finally, two potential mechanisms for the occurrence of drop-outs have been identified. First, random variations in capillary bed perfusion, due to activity for example, can induce transient drops in CGM measurement output of as much as 80 mg/dL. One such event, extending for nearly an hour is visible in Figure 6-7. This mechanism does not appear to have been previously reported and while no remedy is apparent, a diagnosis of the cause is still useful. In addition, externally applied pressure can also induce drop-outs as shown in Figure 6-8. While this mechanism has been anecdotally reported, understanding the physical mechanism that causes pressure-induced drop-outs should allow medical device manufacturers to design future CGM devices in such a way as to minimize or redistribute the transmission of an externally applied pressure gradient to the CGM microenvironment.

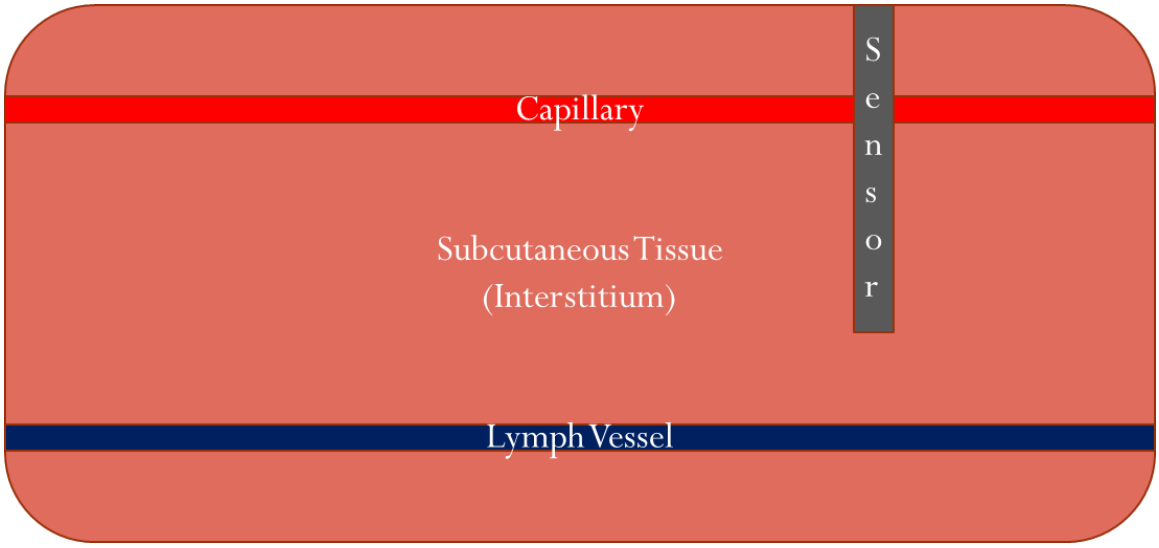

Figure 6-1: Schematic of the Sensing Environment of a CGM Device.

Model Parameter	Value
V_I(L)	4.2
V_L(L)	9.4
P_{cap} (cm/s)	1×10^{-5}
S_{cap} (cm^2/g)	100
P_{lym}	10^{-5}
S_{lym} (cm^2/g)	100
σ_f	2.0×10^{-2}
k_I (min^{-1})	2.0×10^{-3}
k_L (min^{-1})	2.0×10^{-3}
Q (mL/min)	70.0

Table 6-1: Parameters for Lymph-Interstitial Model

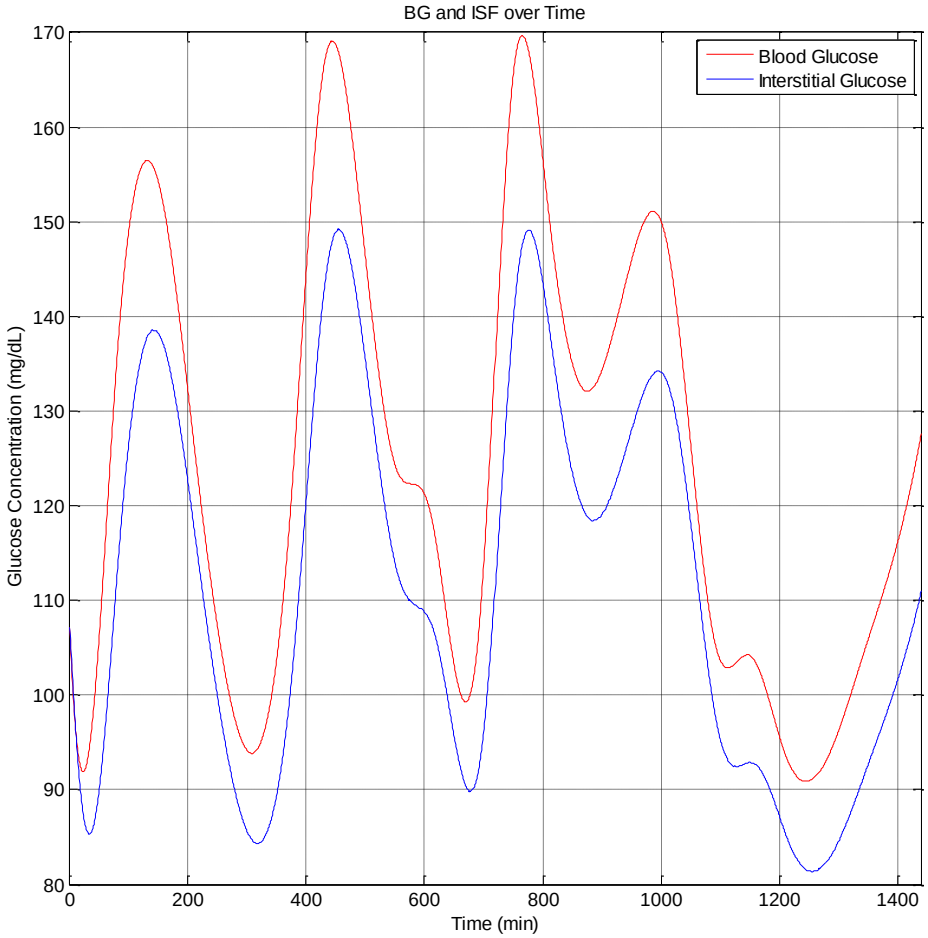

Figure 6-2: Comparison of Blood and Interstitial Glucose Concentrations

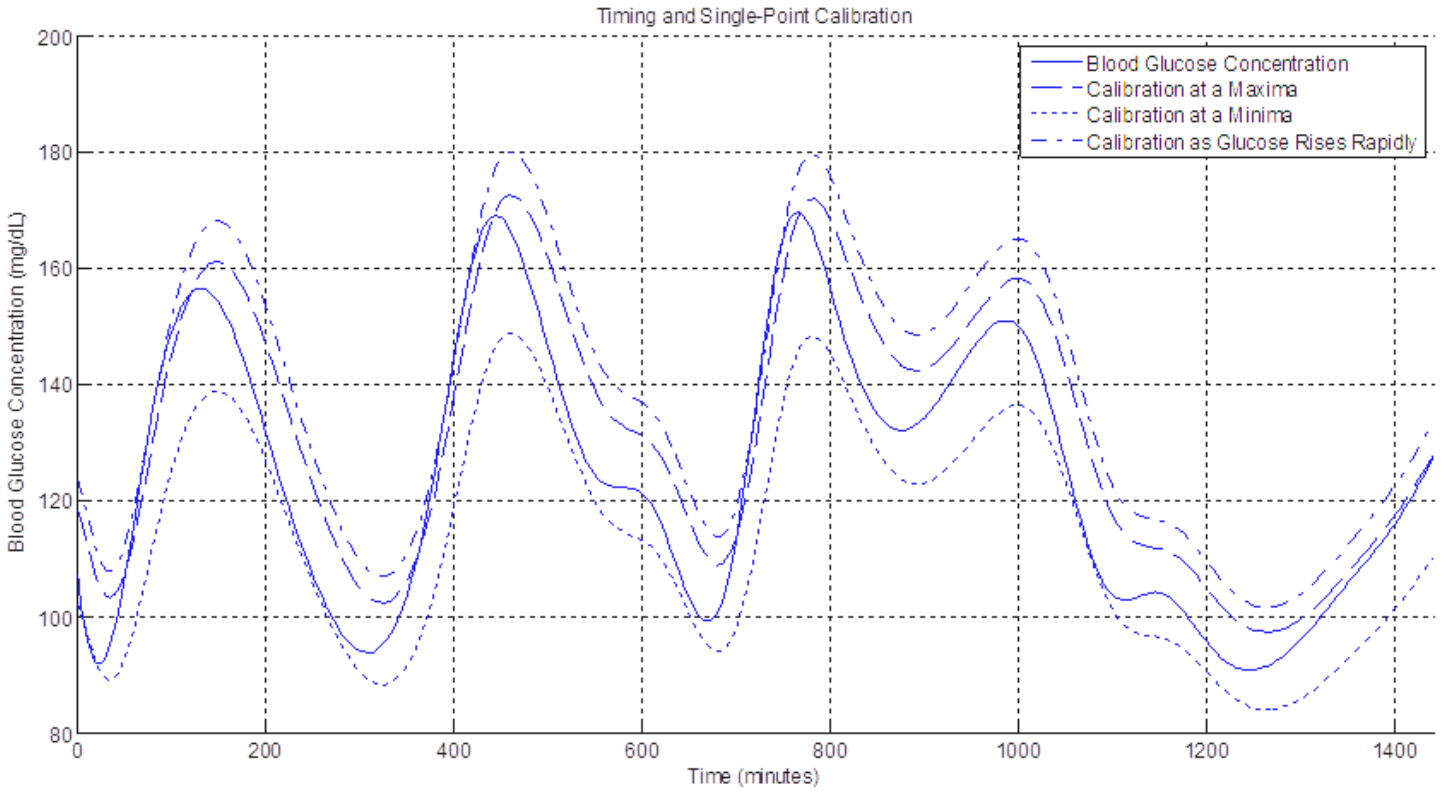

Figure 6-3: The effect of Timing on Single-Point Calibration

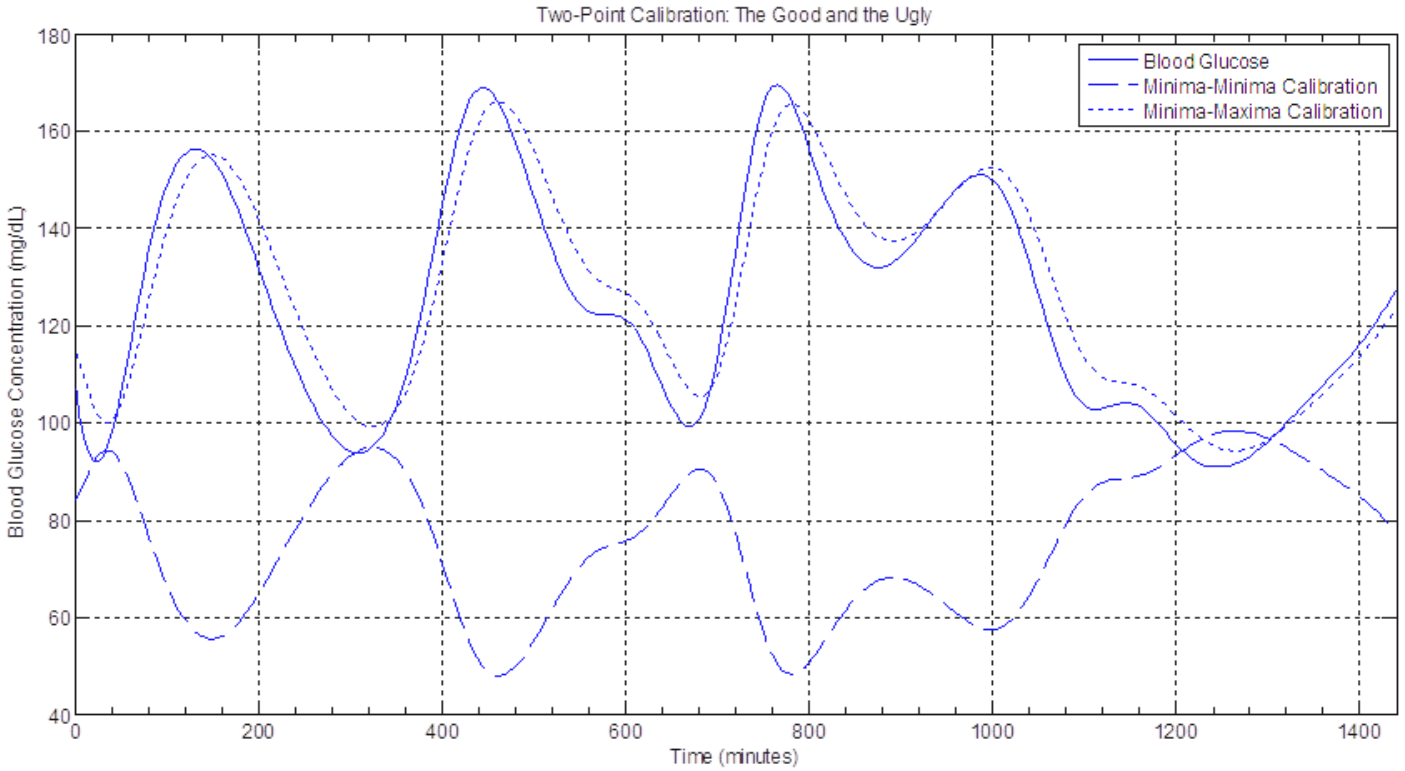

Figure 6-4: Two-Point Calibration of a CGM Device

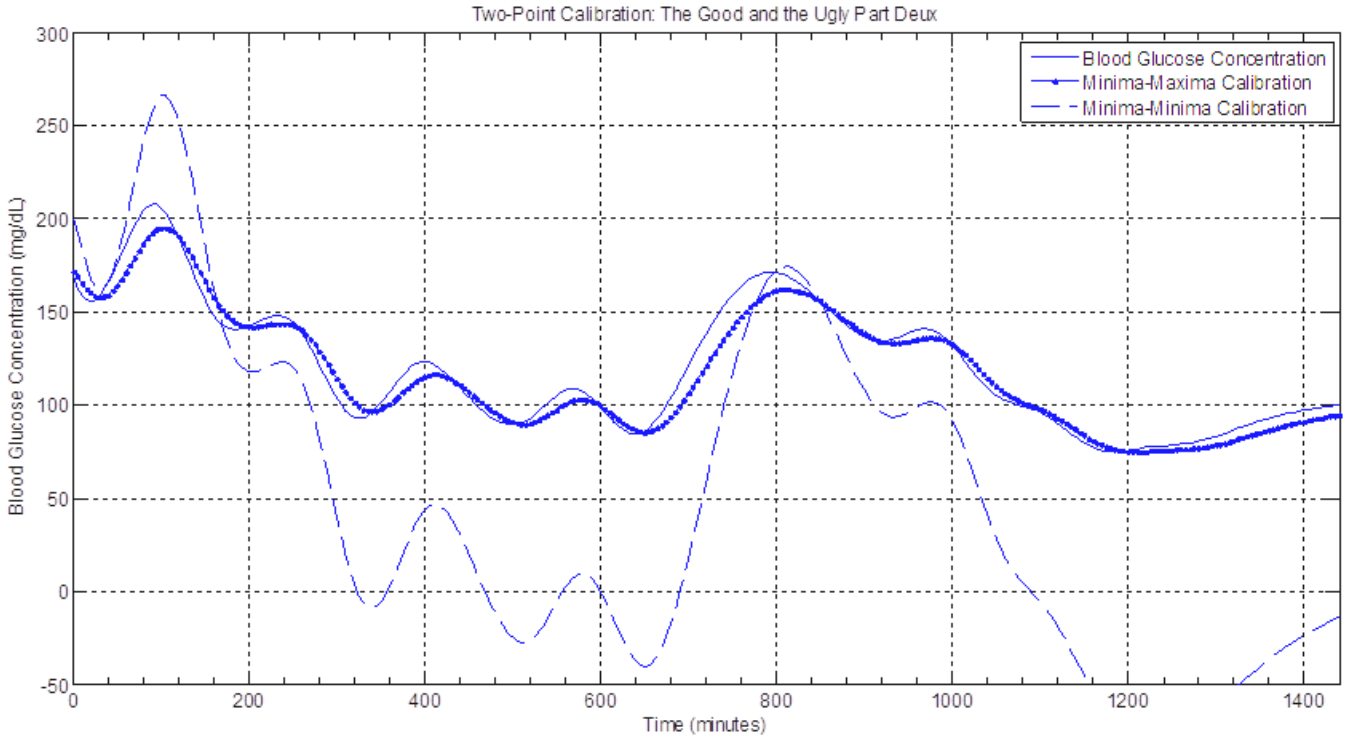

Figure 6-5: Failed Two-Point Calibration of a CGM Device

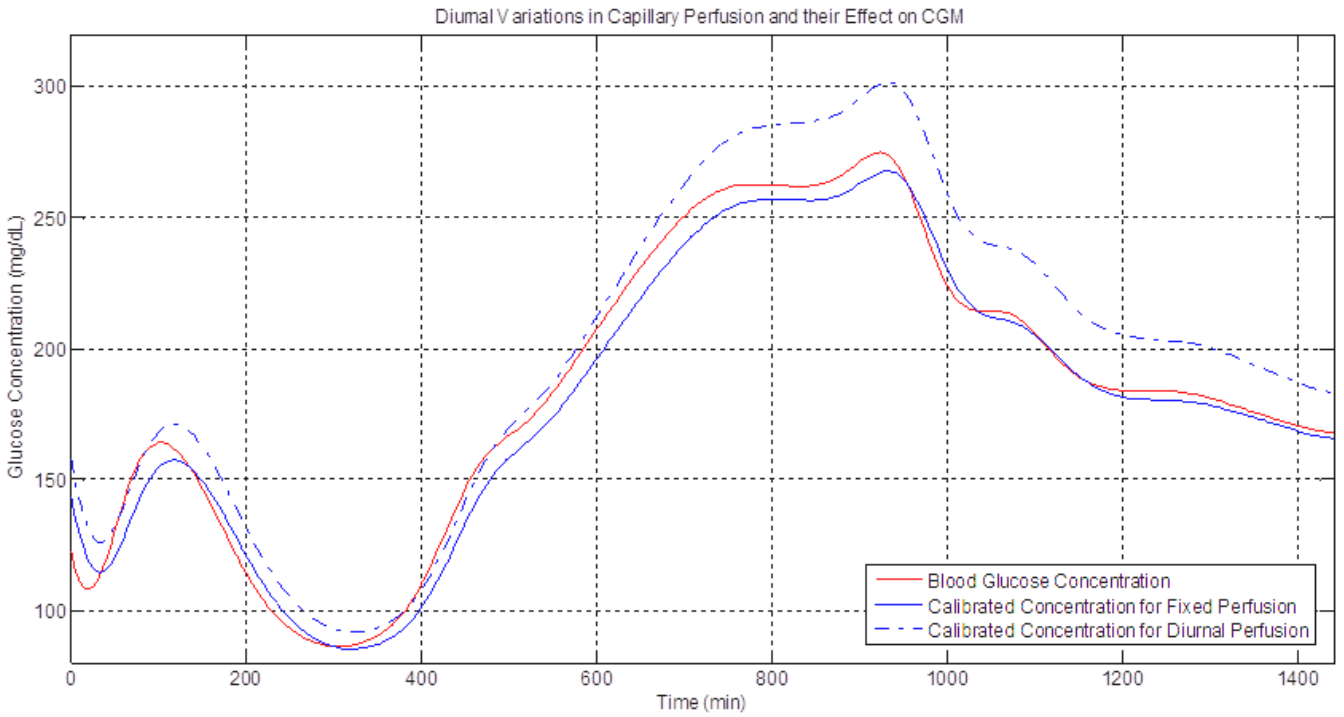

Figure 6-6: CGM Performance – Diurnal Variations in Capillary Perfusion

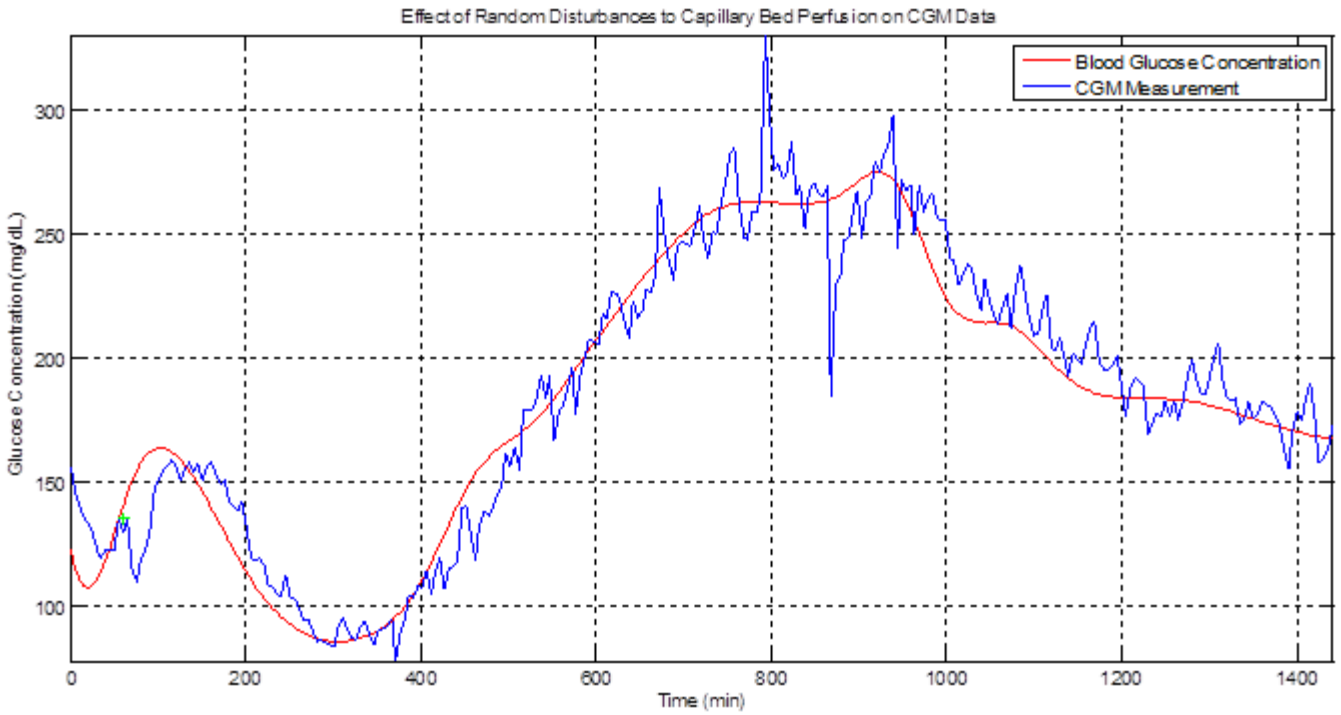

Figure 6-7: CGM Performance – Random Variations in Capillary Perfusion

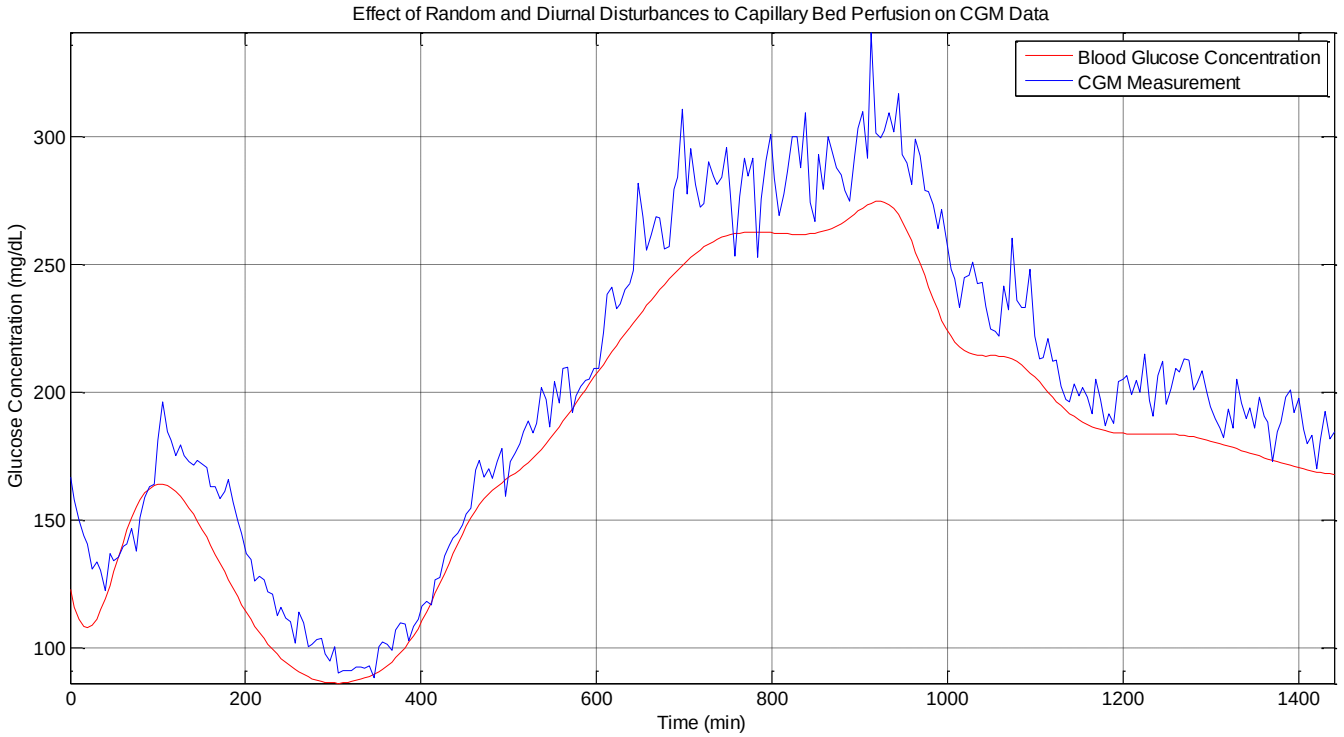

Figure 6-8: CGM Performance – Random and Diurnal Variations in Capillary Perfusion

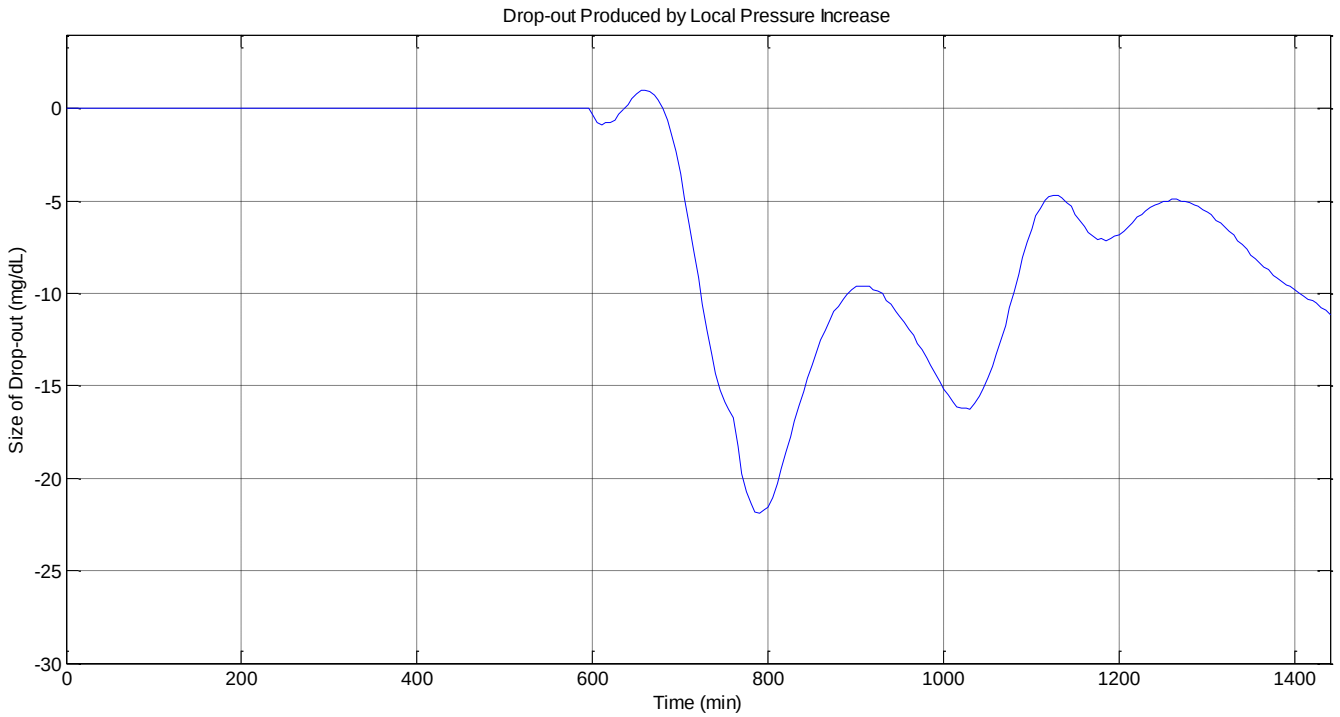

Figure 6-9: Pressure Induced drop-out in CGM Measurements

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Chapter 7: Conclusions

The overall goal of this work was to use the methods of mathematical modeling as well as the recently developed continuous glucose monitors to develop a new way of estimating clinical insulin therapy parameters.

To this end, the Bergman Minimal Model was used to derive control laws defining the insulin sensitivity factor, insulin-to-carbohydrate ratio and basal dose of insulin. It was shown that, despite the simplifying assumptions used to derive them, these control laws performed well under simulation settings. In addition, the predicted insulin sensitivity factor, insulin-to-carbohydrate ratio and basal dose were in excellent agreement with typical values seen in T1DM [1], [2]. Model identifiability was also verified using the Fisher Information Matrix and uncertainty in the clinical insulin therapy parameters was shown to be small.

Having developed a control law, and verifying that its parameters could in principle be identified, we turned our attention to the personalization of our insulin therapy calculator via parameter estimation. Two cohorts of synthetic persons with diabetes were generated using the Bergman Minimal Model and the more complicated Hovorka Model. For both cohorts parameter estimation was performed for two different experimental settings and two different measurement frequencies assuming the availability of CGM measurements. The first experiment was comprised of a single meal and insulin event followed by a period of continuous measurement. This type of experiment could be performed immediately before a physician's visit. The second experiment mimicked a full day of continuous glucose measurement, involving three meals of different size, four total insulin injections and twenty-four hours of recorded measurements, but was also considered simple enough to be performed at home without

supervision. The issue of measurement noise as well as errors in the recording of meal and insulin logs was also simulated.

Overall, parameter estimation in both the Bergman and Hovorka cohorts was successful, although the estimation of basal insulin dose in the Hovorka cohort could not be accomplished. As expected, measurement noise and log errors resulted in degraded parameter estimates. However, the effect of noise on parameter estimation in the Hovorka cohort was smaller than in the Bergman cohort. Given that the Hovorka cohort is viewed as a more realistic test setting, this was a favorable result. In addition, it appears that parameter estimation is only strongly affected by major log errors such as the complete omission of an entry. Errors in the recorded time of a meal or insulin event as well as smaller errors in the magnitude of the event did not produce large errors in parameter estimation.

Finally, parameter estimation using real CGM measurements was successfully performed with one of two available measurement sets. The estimated insulin sensitivity factor, insulin-to-carbohydrate ratio and basal insulin dose agreed well with those inferred from the individuals recording of meal and insulin intake.

The last issue explored was the physiology of CGM measurement and how this physiology may provide a fundamental limit to CGM accuracy and precision. To address this issue, a physiologically-based model of the subcutaneous skin was proposed. This model included compartments to describe the dynamics of both interstitial and lymphatic glucose transport and was parameterized using representative values compiled from the literature. Under stable capillary bed perfusion, it was shown that reasonable calibration schemes can yield blood glucose estimates from CGM that have an error of roughly +/- 5%.

However, as it is known that capillary bed perfusion is variable [3] we sought to quantify how this variability might affect CGM accuracy and precision, considering both diurnal and random variations in capillary bed perfusion. Diurnal variations were shown to increase the average error in CGM measurements by nearly a factor of three, whereas random variations more than doubled average error. In character, diurnal variations tended to cause systematic estimation biases whereas random variations merely increased variance of parameter estimates. As this was only a simulation study, it is difficult to assess whether the physiology of the subcutaneous tissues really holds so much sway over CGM accuracy and precision or whether in real CGM devices other sources of error, including manufacturing variability and device stability, may be more significant. Regardless, the novelty of this analysis should still be valuable if only in sparking discussion.

SIGNIFICANCE FOR THE TREATMENT OF DIABETES

As discussed in Chapter 1, as many as two-thirds of Americans with T1DM fail to achieve ADA targets for good glycemic control, leading to a host of economic and human health consequences. Further, current insulin titration protocols often take a long-time to produce good results and in many cases are unable to bring patients into control [4]–[7].

Alternatives to traditional insulin titration protocols include techniques to augment insulin titration through structured visualization of patient data [8]–[10] as well as complete departures from insulin titration such as the artificial pancreas [11]–[13] and approaches that are somewhere between these extremes such as decision support systems [14]. Further, each of these approaches has its own set of advantages and shortcomings as compared to traditional insulin titration.

In the case of augmented insulin titration protocols, structured visualization techniques make interpreting patient data faster and easier. In addition, because data is collected automatically with a continuous glucose monitor and because one is searching for qualitative patterns, self-reported blood glucose measurements as well as self-reported meal and insulin logs are less important. Given the challenges of correctly estimating meal carbohydrates [15], [16], issues of patient adherence to insulin therapy [17] and the tendency of persons with diabetes to omit hyperglycemic and hypoglycemic blood glucose measurements [18], whether consciously or unconsciously these are non-trivial benefits.

Despite this, augmented insulin titration protocols may still suffer from the main problem facing standard insulin titration protocols. Namely, that good control will still elude as many as 62% of treated patients [6]. In addition, it appears that augmented insulin titration protocols require more skill on the part of providers who must now interpret a large amount of data [8], [19]. Given evidence that many providers will fail to correctly identify abnormal glucose patterns even after training, that 39% of individuals with T1DM are treated by general practitioners and that the general direction in US health care is toward lower cost solutions, the requirement of high provider skill appears to outweigh the other benefits of this approach as a general solution to the shortcomings of insulin titration [20], [21].

Closed-loop insulin delivery systems should in principle require less skill on the part of both patients and practitioners. Similarly, issues of therapy adherence and accurate self-reports of blood glucose measurements as well as insulin and meal events are to a great degree unimportant in closed-loop control. While, the development of more reliable continuous glucose monitors may be a barrier to commercial closed-loop insulin

systems [20], we are confident that industry along with artificial pancreas researchers can resolve all of the technical challenges facing closed-loop systems.

However, the regulatory and economic challenges to closed-loop insulin delivery are considerable. Because there are no predicate devices and because of the high potential for serious adverse events, an artificial pancreas will certainly be a Class III medical device. A recent survey of medical device manufacturers found that the total time from prototype development to FDA approval of a Class III device is on average 9 years [22]. In addition, those familiar with the artificial pancreas estimate that development costs will exceed $170 million [20]. Compounded by the limited adoption of insulin pumps in the US [23], the business case for the artificial pancreas is only compelling if market penetration significantly increases following the device's FDA approval. Further, reimbursement issues which have plagued other devices in the diabetes space may slow market penetration significantly [24].

Finally, decision support systems can have similar advantages and disadvantages depending on their design. In the case of the Diabetes Insulin Guidance System, automated insulin titration, based on self-measured blood glucose, side-steps many of the challenges faced by augmentation of standard insulin titration protocols such as: long convergence times and high provider skill. In addition, if this device can receive FDA approval through the 510k process, the total time to market could be as low as 4.5 years at a cost of $25 million [22]. This compares favorably to the development time and cost profile for the artificial pancreas which will require a PMA.

However, the Diabetes Insulin Guidance system is designed to make the same titrations as a skilled physician [14]. As such, it may still be unable to provide good control for the many patients who struggle with the results of current titration protocols.

The framework developed in this work for calculating and personalizing insulin therapy parameters compares favorably with the above options. Like the Diabetes Insulin Guidance System, our approach can provide titration recommendations very quickly, has no requirements for provider skill and based on private and informal conversations with some FDA officials, may qualify for approval through 510k process. In addition, the results we have presented show that this approach can in provide good control for all individuals—ignoring of course the issue of wanton noncompliance with recommended therapeutic action.

The main limitation at present appears to be the reliance of our approach of self-reported meal and insulin logs. As discussed earlier, individuals with diabetes can fail to maintain good or accurate logs of carbohydrate intake. If this challenge could be resolved, using either smartphone based food logs [25] or smart insulin pens [26] the work of this dissertation could form the basis for a unique and highly differentiated solution to the problem of intensive insulin therapy in T1DM.

COMMERCIAL AND ECONOMIC SIGNIFICANCE

Manufacturers of glucose measurement devices are under tremendous pressure as a result of declining reimbursement and increasing price pressure from competitors [27]. Further, increasing revenue and market share appears to require the development of new and highly differentiated technologies [27]. Finally, as a result of the current climate surrounding health care cost, medical device manufacturers are increasingly required to demonstrate comparative effectiveness to the FDA, insurance companies and health care providers [28]. The combination of these pressures has caused revenue growth for the entire industry to remain flat in the US and has led Roche, a major manufacturer of blood

glucose meters, to consider exiting the market despite having the most popular meter based on patient satisfaction [29], [30].

In light of these facts, the insulin therapy tools developed in this dissertation present a compelling commercial opportunity. Firstly, recalling from Chapter 1 that universally good control of T1DM in the US could yield $4 billion in annual cost savings and that 66% of Americans with T1DM have poor glycemic control, we can calculate that the incremental value for bringing a single individual with T1DM from poor to good control is $6060 per year. As the annual costs of blood glucose measurements supplies currently average $1,000 for an individual with T1DM, even a 10% success rate in moving individuals from poor to good control would create an additional $600 in value per person across a population of individuals with poorly controlled T1DM [31]. This seems almost certain to meet the requirements for comparative effectiveness for any concerned party. Combined with the corresponding improvement in patient outcomes, this new device could very well easily lead to a shift in market share from competing manufacturers.

FUTURE WORK

While it is hoped that this work can be the basis for the next generation of insulin therapy tools, there are still many topics that require further work. Some of these topics include:

- Developing methods to improve parameter estimation techniques. While the approach outlined in this work was adequate, there is certainly room for improvement. Future investigators may wish to consider joint state and parameter estimation which has been used in studies of the artificial

pancreas [32]. Alternatively, "light" design of experiments, to design measurement protocols that can easily be performed at home but, which will provide more informative data may also be fruitful.

- Determining when and how often insulin therapy should be adjusted. It is known that numerous factors can affect insulin requirements on time scales as short as a single day or over several years. Presently, insulin titration algorithms do not account for interday variability in insulin requirements. However, using the tools developed in the present work, it is possible to estimate and personalize insulin therapy from as little as twelve hours of collected data. The questions of if, when and how frequently updates to insulin therapy are necessary need to be answered.
- Developing a system that makes the recording of accurate meal and insulin logs easy. This system could be based on both manual and automated electronic recordings, as for example with a smartphone based meal log and a Bluetooth enabled insulin pen, though it is expected that minimizing user effort will produce more accurate logs.
- Performing human studies to evaluate the performance of the derived insulin therapy parameters. While we were able to show that the proposed insulin therapy framework can be used in the presence of significant model mismatch and for some sets of human data, the only way to truly validate our approach is to test it in humans.
- Performing human or animal studies to assess the effect of variable perfusion on CGM performance. As discussed, we believe that variations in capillary bed perfusion can adversely affect CGM performance. However, it is unclear whether the estimated magnitude of this issue is

correct. In addition, other issues including sensor stability and manufacturing variations may presently be more important. Some simple accuracy studies that account for variations in capillary bed perfusion can determine whether this is a major or minor challenge.

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